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The Western Journal of Medicine

VOLUME 159 • NUMBER 1 JULY 1993

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- Fewer tricyclic effects
- No active metabolites
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Most common adverse events vs placebo include: nausea, somnolence, asthenia, dizziness, insomnia, sweating, tremor, decreased appetite, nervousness, ejaculatory disturbance* and other male genital disorders. Concomitant use of *Paxil* and monoamine oxidase inhibitors (MAOIs) is contraindicated.

*Mostly "ejaculatory delay."

Please see brief summary of prescribing information on adjacent page.

NEW ONCE-DAILY

PAXIL 20 MG

PAROXETINE HCl

FOR DEPRESSION

PAXIL™ (brand of paroxetine hydrochloride)

See complete prescribing information in SmithKline Beecham Pharmaceuticals literature or *PDR*. The following is a brief summary.

INDICATIONS AND USAGE: *Paxil* is indicated for the treatment of depression

CONTRAINDICATIONS: Concomitant use in patients taking monoamine oxidase inhibitors (MAOIs) is contraindicated (See WARNINGS.)

WARNINGS: Interactions with MAOIs may occur. Given the fatal interactions reported with concomitant or immediately consecutive administration of MAOIs and other SSRIs, do not use *Paxil* in combination with a MAOI or within 2 weeks of discontinuing MAOI treatment. Allow at least 2 weeks after stopping *Paxil* before starting a MAOI.

PRECAUTIONS: As with all antidepressants, use *Paxil* cautiously in patients with a history of mania

Use *Paxil* cautiously in patients with a history of seizures. Discontinue it in any patient who develops seizures.

The possibility of suicide attempt is inherent in depression and may persist until significant remission occurs. Close supervision of high-risk patients should accompany initial drug therapy

Write *Paxil* prescriptions for the smallest quantity of tablets consistent with good patient management in order to reduce the risk of overdose.

Reversible hyponatremia has been reported, mainly in elderly patients, patients taking diuretics or those who were otherwise volume depleted.

Clinical experience with *Paxil* in patients with concomitant systemic illness is limited Use cautiously in patients with diseases or conditions that could affect metabolism or hemodynamic responses. Observe the usual cautions in cardiac patients. In patients with severe renal impairment (creatinine clearance <30 mL/min.) or severe hepatic impairment, a lower starting dose (10 mg) should be used

Caution patients about operating hazardous machinery, including automobiles, until they are reasonably sure that *Paxil* therapy does not affect their ability to engage in such activities.

Tell patients 1) to continue therapy as directed; 2) to inform physicians about other medications they are taking or plan to take, 3) to avoid alcohol while taking *Paxil*; 4) to notify their physicians if they become pregnant or intend to become pregnant during therapy, or if they're nursing

Concomitant use of *Paxil* with tryptophan is not recommended.

Use cautiously with warfarin. When administering *Paxil* with cimetidine, dosage adjustment of *Paxil* after the 20 mg starting dose should be guided by clinical effect When co-administering *Paxil* with phenobarbital or phenytoin, no initial *Paxil* dosage adjustment is needed, base subsequent changes on clinical effect. Concomitant use of *Paxil* with drugs metabolized by cytochrome $P_{450}IID_6$ (antidepressants such as nortriptyline, amitriptyline, imipramine, desipramine and fluoxetine; phenothiazines such as thioridazine; Type 1C antiarrhythmics such as propafenone, fecainide and encainide) or with drugs that inhibit this enzyme (e.g., quinidine) may require lower doses than usually prescribed for either *Paxil* or the other drug, approach concomitant use cautiously. Administration of *Paxil* with another tightly protein-bound drug may shift plasma concentrations, resulting in adverse effects from either drug Concomitant use of *Paxil* and alcohol in depressed patients is not advised. Undertake concomitant use of *Paxil* and lithium or digoxin cautiously If adverse effects are seen when co-administering *Paxil* with procyclidine, reduce the procyclidine dose.

In 2-year studies, a significantly greater number of male rats in the 20 mg/kg/day group developed reticulum cell sarcomas vs. animals given doses of 1 or 5 mg/kg/day There was also a significantly increased linear trend across dose groups for the occurrence of lymphoreticular tumors in male rats. Although there was a dose-related increase in the number of tumors in mice, there was no drug-related increase in the number of mice with tumors. The clinical significance of these findings is unknown. There is no evidence of mutagenicity with *Paxil*.

Serotonergic compounds are known to affect reproductive function in animals. Impaired reproductive function in rats (i.e., reduced pregnancy rate, increased pre- and post-implantation losses, decreased viability of pups) was found at *Paxil* doses 15 or more times the highest recommended human dose.

Pregnancy Category B. Reproduction studies performed in rats and rabbits at doses up to 50 and 6 times the maximum recommended human dose have revealed no evidence of teratogenic effects or of selective toxicity to the fetus. However, there are no adequate and well-controlled studies in pregnant women. *Paxil* should be used in pregnancy only if the benefits outweigh the risks. The effect of *Paxil* on labor and delivery in humans is unknown. Paroxetine is secreted in human milk, exercise caution when administering *Paxil* to a nursing woman.

Safety and effectiveness in children have not been established

In worldwide *Paxil* clinical trials, 17% of *Paxil*-treated patients were ≥65 years of age. Pharmacokinetic studies revealed a decreased clearance in the elderly; however, there were no overall differences in the adverse event profile between older and younger patients.

ADVERSE REACTIONS: Incidence in Controlled Trials—*Commonly Observed Adverse Events in Controlled Clinical Trials:* The most commonly observed adverse events associated with the use of *Paxil* (incidence of 5% or greater and incidence for *Paxil* at least twice that for placebo): asthenia (15% vs. 6%), sweating (11% vs. 2%), nausea (26% vs. 9%), decreased appetite (6% vs 2%), somnolence (23% vs. 9%), dizziness (13% vs. 6%), insomnia (13% vs. 6%), tremor (8% vs. 2%), nervousness (5% vs. 3%), ejaculatory disturbance (13% vs 0%) and other male genital disorders (10% vs. 0%). Twenty-one percent (881/4,126) of *Paxil* patients in worldwide clinical trials discontinued treatment due to an adverse event. The most common events (≥1%) associated with discontinuation and considered to be drug related include: somnolence, insomnia, agitation, tremor, anxiety, nausea, diarrhea, dry mouth, vomiting, asthenia, abnormal ejaculation, sweating The following adverse events occurred in 6-week placebo-controlled trials of similar design at a frequency of 1% or more.

Body as a Whole: headache, asthenia, abdominal pain, fever, chest pain, trauma, back pain. **Cardiovascular:** palpitation, vasodilation, postural hypotension **Dermatologic:** sweating, rash **Gastrointestinal:** nausea, dry mouth, constipation, diarrhea, decreased appetite, flatulence, vomiting, oropharynx disorder, dyspepsia, increased appetite. **Musculoskeletal:** myopathy, myalgia, myasthenia. **Nervous System:** somnolence, dizziness, insomnia, tremor, nervousness, anxiety, paresthesia, libido decreased, agitation, drugged feeling, myoclonus, CNS stimulation, confusion **Respiration:** respiratory disorder, yawn, pharyngitis. **Special Senses:** blurred vision, taste perversion **Urogenital System:** ejaculatory disturbance, other male genital disorders, urinary frequency, urination disorder, female genital disorders

Studies show a clear dose dependency for some of the more common adverse events associated with *Paxil* use. There was evidence of adaptation to some adverse events with continued *Paxil* therapy (e.g., nausea and dizziness) Significant weight loss may be an undesirable result of *Paxil* treatment for some patients but, on average, patients in controlled trials had minimal (about 1 lb) loss In placebo-controlled clinical trials, *Paxil*-treated patients exhibited abnormal values on liver function tests no more frequently than placebo-treated patients.

Other Events Observed During the Premarketing Evaluation of *Paxil*: During premarketing assessment, multiple doses of *Paxil* were administered to 4,126 patients, and the following adverse events were reported Note "frequent" = events occurring in at least 1/100 patients; "infrequent"= 1/100 to 1/1000 patients, "rare" = less than 1/1000 patients Events are classified within body system categories and enumerated in order of decreasing frequency using the following definitions It is important to emphasize that although the events occurred during *Paxil* treatment, they were not necessarily caused by it

Body as a Whole: *frequent* chills, malaise; *infrequent*: allergic reaction, carcinoma, face edema, moniliasis, neck pain; *rare*: abscess, adrenergic syndrome, cellulitis, neck rigidity, pelvic pain, peritonitis, ulcer. **Cardiovascular System:** *frequent* hypertension, syncope, tachycardia; *infrequent*: bradycardia, conduction abnormalities, electrocardiogram abnormal, hypotension, migraine, peripheral vascular disorder, *rare* angina pectoris, arrhythmia, atrial fibrillation, bundle branch block, cerebral ischemia, cerebrovascular accident, congestive heart failure, low cardiac output, myocardial infarct, myocardial ischemia, pallor, phlebitis, pulmonary embolus, supraventricular extrasystoles, thrombosis, varicose vein, vascular headache, ventricular extrasystoles. **Digestive System**: *infrequent*: bruxism, dysphagia, eructation, gastritis, glossitis, increased salivation, liver function tests abnormal, mouth ulceration, rectal hemorrhage; *rare*. aphthous stomatitis, bloody diarrhea, bulimia, colitis, duodenitis, esophagitis, fecal impactions, fecal incontinence, gastritis, gastroenteritis, gingivitis, hematemesis, hepatitis, ileus, jaundice, melena, peptic ulcer, salivary gland enlargement, stomach ulcer, stomatitis, tongue edema, tooth caries. **Endocrine System:** *rare*: diabetes mellitus, hyperthyroidism, hypothyroidism, thyroiditis **Hemic and Lymphatic Systems:** *infrequent*. anemia, leukopenia, lymphadenopathy, purpura, *rare*. abnormal erythrocytes, eosinophilia, leukocytosis, lymphedema, abnormal lymphocytes, lymphocytosis, microcytic anemia, monocytosis, normocytic anemia. **Metabolic and Nutritional:** *frequent* edema, weight gain, weight loss; *infrequent*: hyperglycemia, peripheral edema, thirst, *rare*: alkaline phosphatase increased, bilirubinemia, dehydration, gout, hypercholesteremia, hypocalcemia, hypoglycemia, hypokalemia, hyponatremia, SGOT increased, SGPT increased **Musculoskeletal System:** *infrequent* arthralgia, arthritis; *rare*: arthrosis, bursitis, myositis, osteoporosis, tetany **Nervous System:** *frequent* amnesia, CNS stimulation, concentration impaired, depression, emotional lability, vertigo, *infrequent*: abnormal thinking, akinesia, alcohol abuse, ataxia, convulsions, depersonalization, hallucinations, hyperkinesia, hypertonia, incoordination, lack of emotion, manic reaction, paranoid reaction; *rare* abnormal electroencephalogram, abnormal gait, antisocial reaction, choreoathetosis, delirium, delusions, diplopia, drug dependence, dysarthria, dyskinesia, dystonia, euphoria, fasciculations, grand mal convulsion, hostility, hyperalgesia, hypokinesia, hysteria, libido increased, manic-depressive reaction, meningitis, myelitis, neuralgia, neuropathy, nystagmus, paralysis, psychosis, psychotic depression, reflexes increased, stupor, withdrawal syndrome. **Respiratory System:** *frequent* cough increased, rhinitis, *infrequent*. asthma, bronchitis, dyspnea, epistaxis, hyperventilation, pneumonia, respiratory flu, sinusitis, *rare*: carcinoma of lung, hiccups, lung fibrosis, sputum increased **Skin and Appendages:** *frequent*. pruritus; *infrequent*. acne, alopecia, dry skin, ecchymosis, eczema, furunculosis, urticaria; *rare*: angioedema, contact dermatitis, erythema nodosum, maculopapular rash, photosensitivity, skin discoloration, skin melanoma **Special Senses:** *infrequent* abnormality of accommodation, ear pain, eye pain, mydriasis, otitis media, taste loss, tinnitus; *rare* amblyopia, cataract, conjunctivitis, corneal ulcer, exophthalmos, eye hemorrhage, glaucoma, hyperacusis, otitis externa, photophobia **Urogenital System:** *infrequent*. abortion, amenorrhea, breast pain, cystitis, dysmenorrhea, dysuria, menorrhagia, nocturia, polyuria, urethritis, urinary incontinence, urinary retention, urinary urgency, vaginitis; *rare*: breast atrophy, breast carcinoma, breast neoplasm, female lactation, hematuria, kidney calculus, kidney function abnormal, kidney pain, mastitis, nephritis, oliguria, prostatic carcinoma, vaginal moniliasis

Non-U.S. Postmarketing Reports

Voluntary reports of adverse events that have been received since market introduction and may have no causal relationship with *Paxil* include elevated liver function tests (the most severe case was a death due to liver necrosis, and one other case involving grossly elevated transaminases associated with severe liver dysfunction)

DRUG ABUSE AND DEPENDENCE: Controlled Substance Class: *Paxil* is not a controlled substance Evaluate patients carefully for history of drug abuse and observe such patients closely for signs of *Paxil* misuse or abuse (e g , development of tolerance, incrementations of dose, drug-seeking behavior).

BRS-PX L4

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PROGRAM PROFILE

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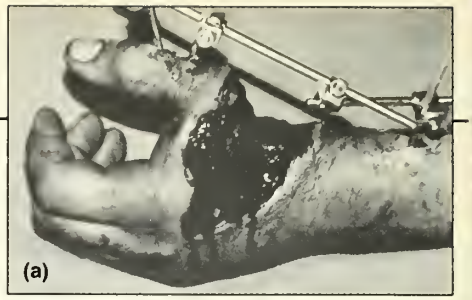

A 27-year-old who sustained a gunshot wound to the base of his thumb was left with (a) a composite defect including lost skin, muscle, tendon, nerve and bone; (b) simultaneous reconstruction of all these missing structures was successfully performed using a tissue flap from his opposite upper arm employing microsurgical techniques.

Microvascular reconstruction has dramatically expanded the field of plastic surgery, opening doors for subspecialists who perform radical resections for the ablation of tumors or who attempt salvage of extremities that have been severely traumatized.

The Reconstructive Surgery Team works closely with specialists in otolaryngology-head and neck surgery, neurosurgery, general surgery, orthopaedics, urology, oncology and rehabilitation. Together they incorporate a variety of procedures, blending innovative techniques that offer the greatest advantage for functional and aesthetic restoration, including:

Hand Surgery

Reconstructive hand surgery is a multifaceted discipline that incorporates techniques employed in several specialties: the treatment of bony injuries, the care of nerves and soft tissue, the restoration of mechanics — joints, tendons, and ligaments. Surgical specialists perform microsurgical replantation and reconstruction of complex hand injuries, and treat congenital hand deformities and hand burns.

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Reconstructive Microsurgery and Complex Wound Management

USC surgeons perform microsurgical free tissue transfer (using vascularized tissue flaps) to manage complex wounds which entails re-establishing circulation of the supplying arteries and draining veins between donor tissue and injury site.

Burn Reconstruction

Specialists in the secondary reconstruction of burn injuries use unique methods of restoring form and function. Surgeons have developed an operation that restores normal neck contour, and another that reconstructs ears, using materials which behave like living tissue. In facial reconstruction, they work to restore balance to the patient's features, focusing not only on skin coverage but also on the structure of the facial skeleton to compensate for the loss of soft tissue and scar contracture.

Treatment of Craniofacial Deformities

The oromandibular region is particularly complex. Through advances in techniques and instrumentation, reconstructive surgeons can move the forehead, change the position of the eyes, realign the jaws and reshape the underlying structure to make dramatic differences in craniofacial deformities.

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PLASTIC SURGEONS

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Susan E. Downey, M.D.
John Gross, M.D.
Larry S. Nichter, M.D.
John F. Reinisch, M.D.
Randolph Sherman, M.D.
Gerald M. Sloan, M.D.
Tad Wellisz, M.D.

Reconstructive Breast Surgery

One alternative, the TRAM flap breast reconstruction procedure, involves the use of abdominal skin and muscles to form a new breast. Other options include autologous tissue replacement, implants, and tissue expanders followed by breast implant.

Post-Cancer Reconstruction

Patients who require extensive disfiguring tumor resection are benefitted by advances in microvascular techniques and osseointegrated implants for facial prosthetic reconstruction. In addition, musculoskeletal tumors in the upper and lower extremities that once required amputation may be treated through limb salvage procedures that incorporate antibiotic therapy, tumor resection, immediate implantation of bone allograft or endoprostheses, and microvascular coverage using free tissue transfer.

Close Communication With Referring Physicians

Members of the University Plastic Surgeons/ Center for Reconstructive Surgery are committed to maintaining close contact with referring physicians to ensure effective patient management for optimal recovery.

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Manuscripts should be sent to the Editor, Linda Hawes Clever, MD, *The Western Journal of Medicine*, 221 Main Street, San Francisco, California 94105. Manuscripts must be original, not previously published, and not under consideration by another publication. If preliminary data were included in another presentation or publication, this should be noted in the cover letter and a copy of that publication should be included.

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- Articles: 2,000 words*
- Conferences and Reviews: 3,000 words*
- Alerts, Notices, and Case Reports: 1,500 words
- Lessons From the Practice: 1,000 words
- Letter to the Editor: 500 words

These totals include references and the abstract but not tables.

All manuscripts will be subject to peer review.

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All authors must sign the letter of transmittal, with one author designated as correspondent and his or her name, address, and telephone number included.

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A letter of transmittal, except for one accompanying a manuscript from US Government employees whose work was done as part of their official duties, must include a paragraph that transfers copyright: "In consideration for reviewing and editing my submission, the author(s) undersigned hereby transfers, assigns, or otherwise conveys all copyright ownership to *The Western Journal of Medicine*, in the event that such work is published by the journal."

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Research or project support should be included as a footnote to the manuscript or in the accompanying cover letter.

Manuscripts concerned with experimental investigation on human subjects must include in the text a statement that all subjects gave their informed consent and that approval of the appropriate ethics committee was obtained.

Acknowledgments will be printed on a select basis—to acknowledge those who contributed to but were not involved in the writing or review of the paper. They should not include persons whose work on the manuscript was a part of their regular duties.

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All values should be in Système International (SI) units, with metric equivalents following in parentheses. Temperature readings should be given in Celsius. Use the generic name of drugs, with the salt or ester given when first used.

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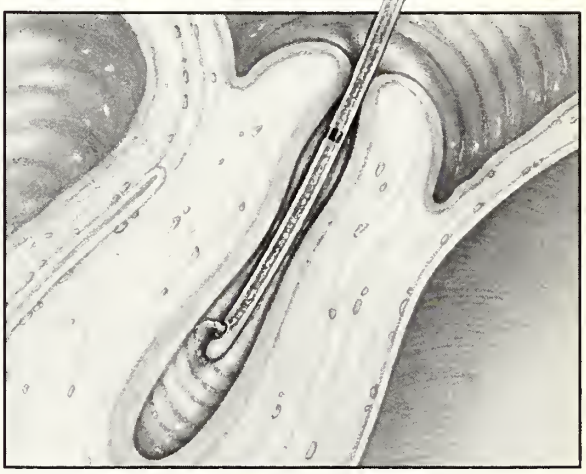

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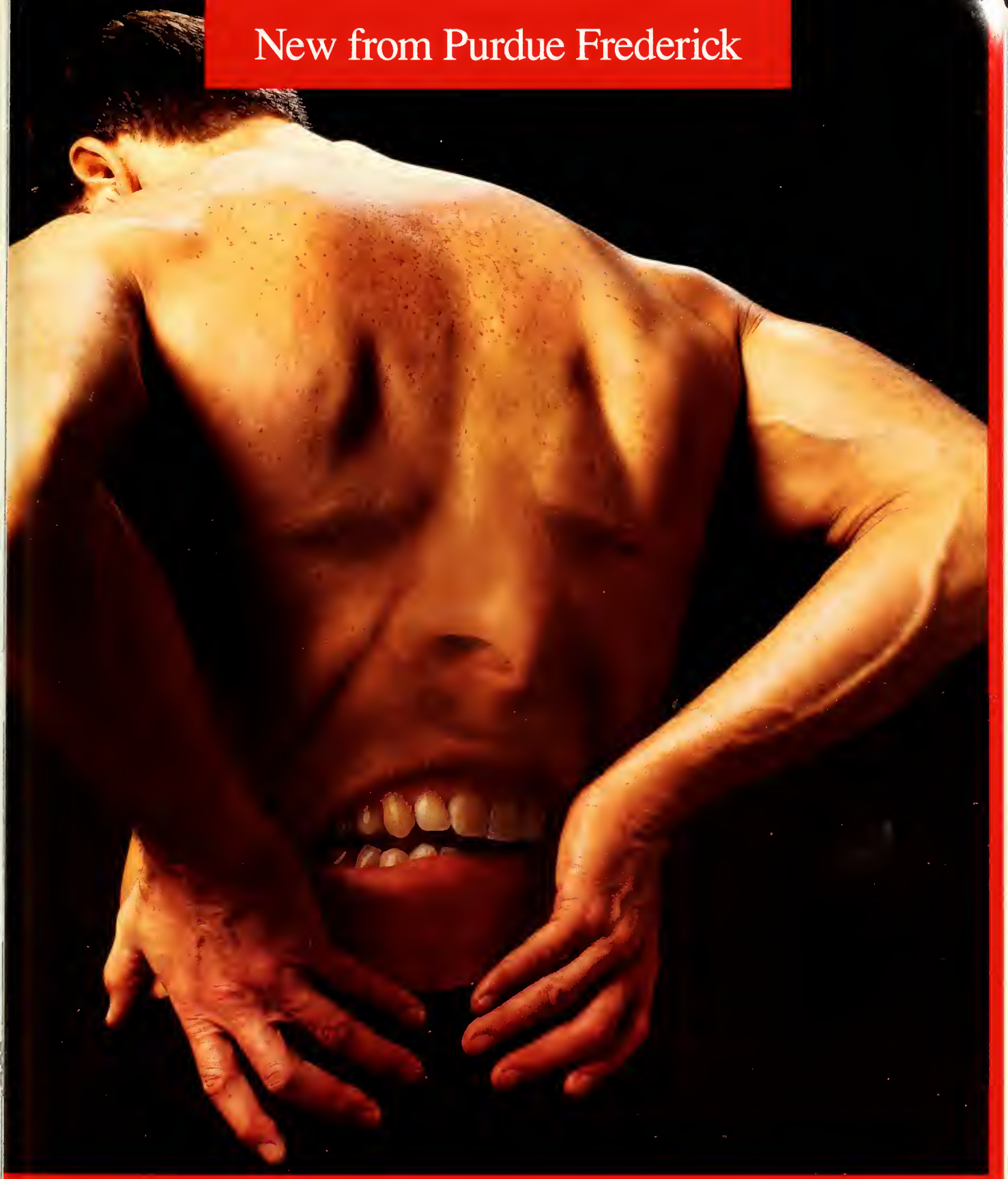

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INDICATIONS: For the relief of moderate to moderately severe pain.

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PRECAUTIONS: General: DHC Plus™ should be given with caution to certain patients such as the elderly or debilitated.

Drug Interactions: The CNS-depressant effects of dihydrocodeine bitartrate may be additive with that of other CNS depressants. See "Warnings."

Usage In Pregnancy: Reproduction studies have not been performed in animals. There is no adequate information on whether this drug may affect fertility in human males and females or has a teratogenic potential or other adverse effect on the fetus.

Usage In Children: Since there is no experience in children who have received this drug, safety and efficacy in children have not been established.

ADVERSE REACTIONS: The most frequently observed reactions include light-headedness, dizziness, drowsiness, sedation, nausea, vomiting, constipation, pruritus, and skin reactions.

DRUG ABUSE AND DEPENDENCE: DHC Plus™ is subject to the provisions of the Controlled Substance Act, and has been placed in Schedule III.

Dihydrocodeine can produce drug dependence of the codeine type and therefore has the potential of being abused. Psychic dependence, physical dependence, and tolerance may develop upon repeated administration of dihydrocodeine, and it should be prescribed and administered with the same degree of caution appropriate to the use of other oral narcotic-containing medications.

OVERDOSAGE: Dihydrocodeine: Signs and Symptoms: Serious overdose with DHC Plus™ is characterized by respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), extreme somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, and sometimes bradycardia and hypotension. In severe overdosage, apnea, circulatory collapse, cardiac arrest and death may occur.

Treatment: Primary attention should be given to the re-establishment of adequate respiratory exchange through provision of a patent airway and the institution of assisted or controlled ventilation. The narcotic antagonist naloxone is a specific antidote against respiratory depression which may result from overdosage or unusual sensitivity to narcotics, including codeine. Therefore, an appropriate dose of naloxone hydrochloride should be administered, preferably by the intravenous route and simultaneously with efforts at respiratory resuscitation. Since the duration of action of dihydrocodeine may exceed that of the antagonist, the patient should be kept under continued surveillance and repeated doses of the antagonist should be administered as needed to maintain adequate respiration.

An antagonist should not be administered in the absence of clinically significant respiratory or cardiovascular depression.

Oxygen, intravenous fluids, vasopressors, and other supportive measures should be employed as indicated.

Gastric emptying may be useful in removing unabsorbed drug.

Acetaminophen: Signs and Symptoms: In acute acetaminophen overdosage, dose-dependent, potentially fatal hepatic necrosis is the most serious adverse effect. Renal tubular necrosis, hypoglycemic coma, and thrombocytopenia may also occur. In adults, hepatic toxicity has rarely been reported with acute overdoses of less than 10 grams and fatalities with less than 15 grams. Importantly, young children seem to be more resistant than adults to the hepatotoxic effect of an acetaminophen overdose. Despite this, the measures outlined below should be initiated in any adult or child suspected of having ingested an acetaminophen overdose.

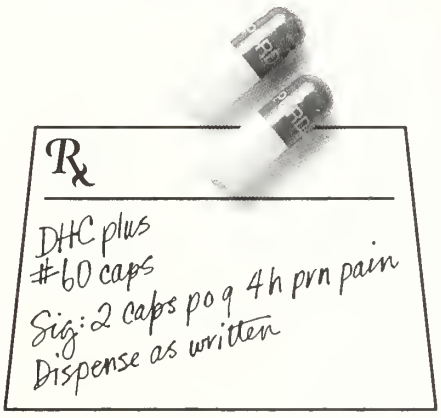
Early symptoms following a potentially hepatotoxic overdose may include: nausea, vomiting, diaphoresis, and general malaise. Clinical and laboratory evidence of hepatic toxicity may not be apparent until 48 to 72 hours post-ingestion.

Treatment: The stomach should be emptied promptly by lavage or by induction of emesis with syrup of ipecac. Patients' estimates of the quantity of a drug ingested are notoriously unreliable. Therefore, if an acetaminophen overdose is suspected, a serum acetaminophen assay should be obtained as early as possible, but no sooner than four hours following ingestion. Liver function studies should be obtained initially and repeated at 24-hour intervals.

The antidote, N-acetylcysteine, should be administered as early as possible, preferably within 16 hours of the overdose ingestion for optimal results, but in any case within 24 hours. Following recovery, there are no residual, structural or functional hepatic abnormalities.

DOSAGE AND ADMINISTRATION: Dosage should be adjusted according to the severity of the pain and the response of the patient. DHC Plus™ is given orally. The usual adult dosage is two capsules every (4) hours as needed for pain.

CAUTION: Federal law prohibits dispensing without prescription.



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ALLERGY/IMMUNOLOGY

July 29-August 1—**A Midsummer Night's Wheeze.** California Society of Allergy and Clinical Immunology at Ojai Valley Inn and Country Club. Thurs-Sun. Contact: CSACI, (310) 597-2661.

September 30-October 2—**1st International Conference on Engineered Vaccines for Cancer and AIDS.** St Francis Memorial Hospital and Northern California Melanoma Center at Fairmont Hotel, San Francisco. Thurs-Sat. Contact: Cass Jones, 7916 Convoy Ct, San Diego 92111, (619) 565-9921.

ANESTHESIOLOGY

September 11-12—**Case Conference in Anesthesia.** California Society of Anesthesiology at Hyatt Hotel, Fisherman's Wharf, San Francisco. Sat-Sun. 9 hrs. $195. Contact: CSA, 1065 E Hillsdale Blvd, Ste 410, Foster City 94404. (800) 345-3691.

October 17-23—**Hawaiian Seminar on Clinical Anesthesia.** California Society of Anesthesiologists at Four Seasons Hotel, Wailea, Maui, Hawaii. Sun-Sat. 23 hrs. $425. Contact: CSA, 1065 E Hillsdale Blvd, Ste 410, Foster City 94404. (800) 345-3691.

November 12-14—**Anesthesiology Update: 1993.** UCD at Monterey Plaza. Fri-Sun. Contact: UCD.

November 19-20—**3rd Annual Pain Management.** UCD at Silverado Country Club, Napa. Fri-Sat. Contact: UCD.

CARDIOLOGY

July 18-22—**Current Concepts in Cardiology.** UCD at Hyatt Lake Tahoe, Incline Village, Nevada. Sun-Thurs. 19 hrs. $400. Contact: UCD.

August 5-7—**Critical Care Cardiology.** UCSF at Sheraton Palace Hotel, San Francisco. Thurs-Sat. 16 hrs. Contact: UCSF.

September 7-10—**Coronary Interventions: 1993.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Tues-Fri. 24 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, 403C, La Jolla 92037. (619) 554-8556.

October 1-3—**Coronary Interventions: 1993.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Fri-Sun. 14 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

October 14-16—**Cardiology Update: 1993.** UCSF at Quail Lodge Resort and Conference Center, Carmel. Thurs-Sat. 12 hrs. $445. Contact: UCSF.

CARDIOVASCULAR DISEASE

August 12-14—**1st Annual Clinical Exercise, Physiology and Cardiac Rehabilitation Conference.** American College of Cardiology at Holiday Inn, Palo Alto. Thurs-Sat. 20.5 hrs. Contact: ACC, 9111 Old Georgetown Rd, Bethesda, MD 20814-1699. (800) 257-4739.

September 28-October 1—**47th Annual Fall Conference and Scientific Sessions of the Council for High Blood Pressure Research.** American Heart Association at Hyatt Regency, San Francisco. Tues-Fri. 21 hrs. Contact: AHA, 7272 Greenville Ave, Dallas, TX 75231. (214) 706-1511.

DERMATOLOGY

July 20-24—**Superficial Anatomy and Cutaneous Surgery.** Scripps Clinic and Research Foundation and UCSD at UCSD Campus, San Diego. Tues-Sat. 36 hrs. $1100. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

July 29-31—**Workshop in Dermatopathology.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Thurs-Sat. 20 hrs. $435. Contact: James Graham, MD, Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

August 9-11—**Dermatology for the Non-Dermatologist.** Continuing Medical Education Associates at Hotel del Coronado, San Diego. Mon-Wed. 20 hrs. $450. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

EMERGENCY MEDICINE

August 7-10—**Kaiser Permanente Emergency Medicine Conference.** Kaiser Permanente at Grand Hyatt Union Square, San Francisco. Sat-Tues. $275. Contact: KPEM Conference, PO Box 7131, Corte Madera 94976-7131. (415) 927-7450.

August 16-20—**Emergency Medicine Symposium II.** UCSD. Mon-Fri. 32 hrs. $495. Contact: UCSD.

October 15-17—**Advances in Emergency Medicine.** UCSD at Hyatt Regency, La Jolla. Fri-Sun. 20 hrs. $450. Contact: UCSD.

October 18-22—**Emergency Medicine Symposium I.** UCSD at San Diego Hilton Beach and Tennis Resort. Mon-Fri. 32 hrs. $495. Contact: UCSD.

October 21-23—**Traumatic Brain Injury.** UCD at Hilton Hotel, Sacramento. Thurs-Sat. Contact: UCD.

November 8-12—**Emergency Medicine Symposium III.** UCSD at San Diego Hilton. Mon-Fri. 32 hrs. $495. Contact: UCSD.

KEY TO ABBREVIATIONS

CMA — California Medical Association
Contact: Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690. (415) 541-0900.

CPMC — California Pacific Medical Center
Contact: Continuing Education, California Pacific Medical Center, PO Box 7999, San Francisco 94120. (415) 923-3441.

DREW — Charles R. Drew Postgraduate Medical School
Contact: Herbert M. Thomas, MD, MPH, Director of CME, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th St, Los Angeles 90059. (213) 603-3183.

LLU — Loma Linda University
Contact: James I. Couperus, MD, Associate Dean for Educational Affairs, Loma Linda University School of Medicine, Loma Linda 92350.

STAN — Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Medical School Office Building, Suite X-365, Stanford 94305-6114 (415) 723-5594

UCD — University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, 2701 Stockton Blvd, Sacramento 95817. (916) 734-5390.

UCI — University of California, Irvine
Contact: Melvin I. Marks, MD, Director, Memorial/UCI Center for Health Education, Long Beach Memorial Medical Center, 2801 Atlantic Ave, PO Box 1428, Long Beach, California 90801-1428. (213) 595-3811.

UCLA — University of California, Los Angeles Extension
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, PO Box 24902, UCLA, Los Angeles 90024. (310) 825-8423.

UCSD — University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (619) 534-3940.

UCSF — University of California, San Francisco
Contact: Janet Johnson, Administrative Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 476-4251.

USC — University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 1975 Zonal Ave, KAM314, Los Angeles 90033. (800) 872-1119.

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FAMILY PRACTICE/PRIMARY CARE

July 22-24—**Primary Care for the 21st Century.** Mercy Health Centers at Catamaran Resort Hotel, San Diego. Thurs-Sat. 17 hrs. $250. Contact: Shirley Kolkey (619) 271-6673.

August 6-8—**Cardiology for the Family Physician and Internist.** Continuing Medical Associates at Hotel del Coronado, San Diego. Fri-Sun. 20 hrs. $450. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

August 20-22—**Office Gynecology for the Primary Care Physician.** SDSU at Hyatt Islandia, San Diego. Fri-Sun. 20 hrs. $450. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

August 20-22—**Primary Care Medicine: A Practical Approach.** Scripps Clinic at Le Meridien San Diego. Fri-Sun. 16 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

September 11—**Primary Care Issues in Cardiac & Vascular Disease.** Alta Bates Medical Center at Claremont Resort, Berkeley. Sat. 7 hrs. $75. Contact: Mary Grim, (510) 204-1420.

October 6-8—**Primary Care Medicine: Principles and Practice.** UCSF at Nikko Hotel, San Francisco. Wed-Fri. 20 hrs. $485. Contact: UCSF.

October 6-9—**15th Semiannual Wound Management Workshop for Primary Care.** UCSD at San Diego Hilton. 17 hrs. $475. Contact: UCSD.

November 10-13—**North American Primary Care Research Group—Research Frontiers in Primary Care and Prevention.** UCSD at Hyatt Islandia on Mission Bay, San Diego. Wed-Sat. 23 hrs. $400. Contact: UCSD.

December 2-4—**Obstetrics and Gynecology Conference.** University of Nebraska at Bally's Las Vegas. Thurs-Sat. $275. Contact: University of Nebraska Medical Center, 600 S 42nd St, Omaha, NE 68198-5651. (402) 559-4152 or (800) 642-1095.

GERIATRICS

November 8-10—**Geriatrics Update: 1993.** Sharp Memorial Hospital at Loew's Coronado Bay Resort, San Diego. Mon-Wed. 20 hrs. $425. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

INFECTIOUS DISEASES

September 2-5—**HIV, AIDS, and Women.** UCSD at La Jolla Marriott. Thurs-Sun. 15 hrs. $200. Contact: UCSD.

November 5-7—**Advances in Infectious Disease.** Sharp Memorial Hospital at Loew's Coronado Bay Resort, San Diego. Fri-Sun. 20 hrs. $425. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

October 1-3—**Gastroenterology: Advances in Diagnosis and Management.** UCSF at Ana Hotel, San Francisco. Fri-Sun. 18 hrs. $430. Contact: UCSF.

October 14-16—**Recent Advances in Pulmonary and Critical Care Medicine.** UCSF at Ana Hotel, San Francisco. Thurs-Sat. 16 hrs. $415. Contact: UCSF.

INTERNAL MEDICINE

August 22-27—**New Advances in Internal Medicine.** UCD at Hyatt Regency, Monterey. Sun-Fri. 25 hrs. Contact: UCD.

NEUROLOGY

August 5-7—**5th Annual New Advances in Common Neurological Disorders.** UCSD at Catamaran Hotel, San Diego. 14 hrs. $350. Contact: UCSD.

OB/GYN

July 25-28—**In-Vitro Fertilization and Embryo Transfer: A Comprehensive Update—1993.** UCLA at Four Seasons Biltmore Hotel, Santa Barbara. Sun-Wed. 20.5 hrs. $521-$695. Contact: UCLA Extension.

November 20—**Infertility Update VII.** Scripps Clinic and Research Foundation, La Jolla. Sat. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

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OCCUPATIONAL/ENVIRONMENTAL

July 26-30—**Sports Medicine 1993.** UCSD at San Diego Princess Resort. Mon-Fri. 21 hrs. $350. Contact: UCSD.

October 25-29—**Occupational and Environmental Medicine.** UCSF at Miyako Hotel, San Francisco. Mon-Fri. 40 hrs. $700. Contact: UCSF.

ONCOLOGY

October 25-27—**17th Annual Cancer Symposium.** Scripps Memorial Hospital at Sheraton Harbor Island Hotel, San Diego. Mon-Wed. 20 hrs. $390. Contact: Cancer Symposium Conference Office, PO Box 16502, Irvine 92713-6338. (800) 321-6338.

November 4-5—**Growth Control, Signal Transduction and Oncogenesis.** UCLA at Beverly Hilton Hotel, Beverly Hills. Thurs-Sat. 12.75 hrs. $113-$150. Contact: UCLA Extension.

November 5-6—**American College of Surgeons: Cancer Management Course.** UCD at Cancer Center Auditorium, Sacramento. Fri-Sat. 13 hrs. $400. Contact: UCD.

OPHTHALMOLOGY

September 18—**General Medicine Update for Ophthalmologists.** UCD at Cancer Center Auditorium, Sacramento. Sat. Contact: UCD.

October 16—**Annual Ophthalmology Update: 1993.** UCD at Cancer Auditorium at Sacramento. Sat. Contact: UCD.

ORTHOPAEDICS

July 25-31—**An Update in Orthopaedics.** Kaiser Permanente at Hyatt Wailea, Maui, Hawaii. Sun-Sat. 20 hrs. $395-$495. Contact: Scott Waters, 1800 Harrison, 20th Fl, Oakland 94612. (510) 987-3087.

September 29-October 2—**6th Annual Comprehensive Foot and Ankle Course.** American Academy of Orthopaedic Surgeons at Sheraton Palace Hotel/Summit Health Education Center, San Francisco. Wed-Sat. Contact: AAOS, 6300 N River Rd, Rosemont, IL 60018-4262. (800) 346-2207.

October 18-20—**The Knee and Shoulder in Sports.** American College of Sports Medicine at Westin Maui, Kaanapali Beach, Maui, Hawaii. Mon-Wed. 13 hrs. $300. Contact: Stuart Zeman, MD. (800) 346-3277.

October 29-30—**Revision Total Hip in the 1990s.** American Academy of Orthopaedic Surgeons at US Grant Hotel, San Diego. Fri-Sat. Contact: AAOS, 6300 N River Rd, Rosemont, IL 60018-4262. (800) 346-2207.

November 5-9—**Fractures of the Pelvis and Acetabulum.** American Academy of Orthopaedic Surgeons at Marriott's Rancho Las Palmas Resort and Country Club Annenberg Center, Eisenhower Medical Center, Rancho Mirage. Fri-Tues. Contact: AAOS, 6300 N River Rd, Rosemont, IL 60018-4262. (800) 346-2207.

December 3-5—**Review and Update for Practicing Orthopaedic Surgeons.** American Academy of Orthopaedic Surgeons at Sheraton Palace Hotel, San Francisco. Fri-Sun. Contact: AAOS, 6300 N River Rd, Rosemont, IL 60018-4262. (800) 346-2207.

December 8-12—**American Back Society Meeting.** American Back Society at Hyatt Regency Embarcadero, San Francisco. Wed-Sun. Contact: ABS, 2647 E 14th St, Ste 401, Oakland 94601. (510) 536-9929.

OTOLARYNGOLOGY

November 4-6—**The San Francisco Otology, Neurotology, and Skull Base Surgery Update—1993.** UCSF at Ritz-Carlton Hotel, San Francisco. Thurs-Sat. 22 hrs. $395. Contact: UCSF.

PATHOLOGY

August 7-14—**14th Annual Comprehensive Fine Needle Biopsy Course.** UCSF at Ritz-Carlton, Kapalua, Maui, Hawaii. 1 wk. 27 hrs. $950. Contact: UCSF.

October 2—**33rd Annual Scientific Symposium on Kidney Disease.** National Kidney Foundation of Southern California at Stouffer Esmeralda Resort, Indian Wells. Sat. Contact: Sylvie Tarro. (310) 641-8152.

October 25-29—**19th Annual Lukes Conference: Diagnostic Approaches to Lymphoproliferative Disorders.** Fri-Tues. 27 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

PEDIATRICS

August 23-25—**Pediatrics Update: 1993.** SDSU at Hyatt Islandia, San Diego. Mon-Wed. 20 hrs. $450. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

PSYCHIATRY

August 3-7—**Impulse Control Disorders and Addictions: Update and Review.** Southern California Neuropsychiatric Institute at Mauna Kea Beach Hotel, The Big Island, Hawaii. Tues-Sat. 24 hrs. Contact: Ann McCormick, 6794 La Jolla Blvd, La Jolla 92037. (619) 454-2102.

RADIOLOGY

August 12-15—**Physics of Diagnostic Radiology, Nuclear Medicine, and Radiation Biology.** UCSD on Campus. Thurs-Sun. Contact: UCSD.

October 18-20—**Radiology for the Non-Radiologists.** UCSD at Hyatt Regency, San Diego. Mon-Wed. 20 hrs. $450. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

October 23-24—**MRI of the Musculoskeletal System.** UCSD at Hotel del Coronado, San Diego. Sat-Sun. 9 hrs. $275. Contact: UCSD.

October 25-29—**18th Annual San Diego Postgraduate Radiology Course.** UCSD at Hotel del Coronado, San Diego. Mon-Fri. 25 hrs. $595. Contact: UCSD.

October 29-31—**Annual Interventional Radiology Course.** UCSD at Hotel del Coronado, San Diego. Fri-Sun. 16 hrs. $375. Contact: UCSD.

November 12-14—**Advanced Seminars in Diagnostic Imaging.** UCSD at Ritz-Carlton, Laguna Niguel. Fri-Sun. 20 hrs. $500. Contact: UCSD.

RISK MANAGEMENT

July 19-20—**High Risk Emergency Medicine: Preventing Malpractice.** CAL/ACEP Emergency Medical Group at San Diego. Mon-Tues. 15 hrs. $345-$495. Contact: Kathy Hester, Risk Management Programs, (800) 451-7475.

September 27-28—**High Risk Emergency Medicine: Preventing Malpractice.** CAL/ACEP at Las Vegas, Nevada. Mon-Tues. 15 hrs. $345-$495. Contact: Kathy Hester, (800) 451-7475.

SURGERY

August 11-14—**7th International Symposium on the Latest Advances in Cosmetic Surgery of the Face.** Foundation for Facial Plastic Surgery at Hyatt Newporter Resort, Newport Beach. Wed-Sat. 25 hrs. $795. Contact: Angela O'Mara, (714) 759-7678.

VASCULAR DISEASE

October 4-8—**A Comprehensive Review of What's New in Vascular Surgery.** UCLA at Miramar Sheraton Hotel, Santa Monica. Mon-Fri. 34 hrs. $487-$650. Contact: UCLA Extension.

GENERAL/MULTIDISCIPLINARY

July 30-31—**Managed Care in an Era of Reform: The Health Care Experts Speak.** UCLA at Law School, Westwood. Fri-Sat. 5 hrs. $290. Contact: UCLA Extension.

October 14-17—**Women in Medicine.** UCSD at San Diego Hilton. Thurs-Sun. 15 hrs. $300. Contact: UCSD.

October 27-31—**CME/Golf Meeting.** Nevada Academy of Family Physicians Las Vegas Chapter at Rio Hotel, Las Vegas. Wed-Sun. 23 hrs. $75. Contact: Barbara Bolling, PO Box 27713, Las Vegas, NV 89126-1713. (702) 647-0117.

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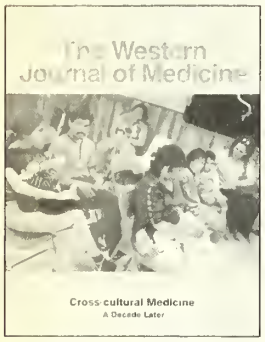

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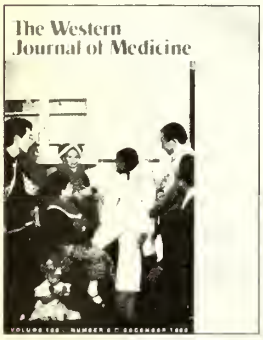

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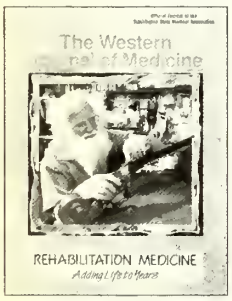

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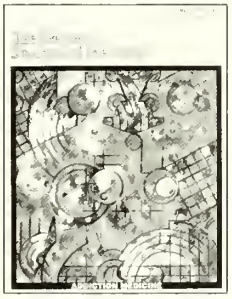

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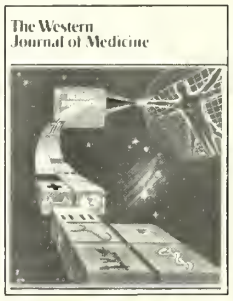

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ALTACE is contraindicated in patients who are hypersensitive to this product and in patients with a history of angioedema related to previous treatment with an ACE inhibitor.

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INDICATIONS AND USAGE: ALTACE is indicated for the treatment of hypertension. It may be used alone or in combination with thiazide diuretics.

In using ALTACE, consideration should be given to the fact that another angiotensin converting enzyme inhibitor, captopril, has caused agranulocytosis, particularly in patients with renal impairment or collagen-vascular disease. Available data are insufficient to show that ALTACE does not have a similar risk. (See WARNINGS.)

CONTRAINDICATIONS: ALTACE is contraindicated in patients who are hypersensitive to this product and in patients with history of angioneurotic edema.

WARNINGS: ***Angioedema:*** Angioedema of the face, extremities, lips, tongue, glottis, and larynx has been reported in patients treated with angiotensin converting enzyme inhibitors. Angioedema associated with laryngeal edema can be fatal. If laryngeal stridor or angioedema of the face, tongue, or glottis occurs, treatment with ALTACE should be discontinued and appropriate therapy instituted immediately. **Where there is involvement of the tongue, glottis, or larynx, likely to cause airway obstruction, appropriate therapy, e.g., subcutaneous epinephrine solution 1:1,000 (0.3 mt to 0.5 mt) should be promptly administered.** (See ADVERSE REACTIONS.)

Hypotension: ALTACE can cause symptomatic hypotension, after either the initial dose or a later dose when the dosage has been increased. Like other ACE inhibitors, ramipril has been only rarely associated with hypotension in uncomplicated hypertension. Symptomatic hypotension is most likely to occur in patients who have been volume- and/or salt-depleted as a result of prolonged diuretic therapy, dietary salt restriction, dialysis, diarrhea, or vomiting. Volume and/or salt depletion should be corrected before initiating therapy with ALTACE.

In patients with congestive heart failure, with or without associated renal insufficiency, ACE inhibitor therapy may cause excessive hypotension, which may be associated with oliguria or azotemia and, rarely, with acute renal failure and death. In such patients, ALTACE therapy should be started under close medical supervision, they should be followed closely for the first 2 weeks of treatment and whenever the dose of ramipril or diuretic is increased.

If hypotension occurs, the patient should be placed in a supine position and, if necessary, treated with intravenous infusion of physiological saline. ALTACE treatment usually can be continued following restoration of blood pressure and volume.

Neutropenia/Agranulocytosis: Another angiotensin converting enzyme inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression, rarely in uncomplicated patients, but more frequently in patients with renal impairment, especially if they also have a collagen-vascular disease such as systemic lupus erythematosus or scleroderma. Available data from clinical trials of ramipril are insufficient to show that ramipril does not cause agranulocytosis at similar rates. Monitoring of white blood cell counts should be considered in patients with collagen-vascular disease, especially if the disease is associated with impaired renal function.

Fetal/Neonatal Morbidity and Mortality: ACE inhibitors can cause fetal and neonatal morbidity and death when administered to pregnant women. More than 100 cases have been reported in the world literature. When pregnancy is detected, ACE inhibitors should be discontinued as soon as possible.

The use of ACE inhibitors during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible and irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to the ACE-inhibitor exposure.

These adverse effects do not appear to have resulted from intrauterine ACE-inhibitor exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to ACE inhibitors only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should make every effort to discontinue the use of ALTACE as soon as possible.

Rarely (probably less often than once in every thousand pregnancies), no alternative to ACE inhibitors will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examination should be performed to assess the intra-amniotic environment.

If oligohydramnios is observed, ALTACE should be discontinued unless it is considered lifesaving for the mother. Contraction stress testing (CST), a non-stress test (NST), or biophysical profiling (BPP) may be appropriate depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not be apparent until after the fetus has sustained irreversible injury.

Infants with histories of *in utero* exposure to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function. ALTACE, which crosses the placenta, can be removed from the neonatal circulation by these means, but limited experience has not shown that such removal is central to the treatment of these infants.

No teratogenic effects of ALTACE were seen in studies of pregnant rats, rabbits, and cynomolgus monkeys. On a mg/kg basis, the doses used were up to 2,500 times (in rats), 6.25 times (in rabbits), and 1.250 times (in monkeys) the maximum recommended human dose.

PRECAUTIONS: ***General:*** *Impaired Renal Function.* As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe congestive heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with angiotensin converting enzyme inhibitors, including ALTACE, may be associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death. In hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine may occur. Experience with another angiotensin converting enzyme inhibitor suggests that these increases are usually reversible upon discontinuation of ALTACE and/or diuretic therapy. In such patients renal function should be monitored during the first few weeks of therapy. Some hypertensive patients with no apparent pre-existing renal vascular disease have developed increases in blood urea nitrogen and serum creatinine, usually minor and transient, especially when ALTACE has been given concomitantly with a diuretic. This is more likely to occur in patients with pre-existing renal impairment. Dosage reduction of ALTACE and/or discontinuation of the diuretic may be required.

Evaluation of the hypertensive patient should always include assessment of renal function.

Hyperkalemia. In clinical trials, hyperkalemia (serum potassium greater than 5.7 mEq/L) occurred in approximately 1% of hypertensive patients receiving ALTACE. In most cases, these were isolated values, which resolved despite continued therapy. None of these patients was discontinued from the trials because of hyperkalemia. Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with ALTACE. (See DRUG INTERACTIONS.)

Cough: Cough has been reported with the use of ACE inhibitors. Characteristically, the cough is nonproductive, persistent and resolves after discontinuation of therapy. ACE inhibitor-induced cough should be considered as part of the differential diagnosis of cough.

Impaired Liver Function: Since ramipril is primarily metabolized by hepatic esterases to its active moiety, ramiprilat, patients with impaired liver function could develop markedly elevated plasma levels of ramipril. No formal pharmacokinetic studies have been carried out in hypertensive patients with impaired liver function.

Surgery/Anesthesia: In patients undergoing surgery or during anesthesia with agents that produce hypotension, ramipril may block angiotensin II formation that would otherwise occur secondary to compensatory renin release. Hypotension that occurs as a result of this mechanism can be corrected by volume expansion.

Information for Patients: *Angioedema:* Angioedema, including laryngeal edema, can occur with treatment with ACE inhibitors, especially following the first dose. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, eyes, lips, tongue, or difficulty in breathing) and to take no more drug until they have consulted with the prescribing physician.

Symptomatic Hypotension: Patients should be cautioned that lightheadedness can occur, especially during the first days of therapy, and it should be reported. Patients should be told that if syncope occurs, ALTACE™ (ramipril) should be discontinued until the physician has been consulted.

All patients should be cautioned that inadequate fluid intake or excessive perspiration, diarrhea, or vomiting can lead to an excessive fall in blood pressure, with the same consequences of lightheadedness and possible syncope.

Hyperkalemia: Patients should be told not to use salt substitutes containing potassium without consulting their physician.

Neutropenia: Patients should be told to promptly report any indication of infection (e.g., sore throat, fever), which could be a sign of neutropenia.

Pregnancy: Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to ACE inhibitors, and they should also be told that these consequences do not appear to have resulted from intrauterine ACE-inhibitor exposure that has been limited to the first trimester. These patients should also be asked to report pregnancies to their physicians as soon as possible.

Drug Interactions: *With Diuretics:* Patients on diuretics, especially those in whom diuretic therapy was recently instituted, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with ALTACE. The possibility of hypotensive effects with ALTACE can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with ALTACE. If this is not possible, the starting dose should be reduced.

With Potassium Supplements and Potassium-Sparing Diuretics: ALTACE can attenuate potassium loss caused by thiazide diuretics. Potassium-sparing diuretics (spironolactone, amiloride, triamterene, and others) or potassium supplements can increase the risk of hyperkalemia. Therefore, if concomitant use of such agents is indicated, they should be given with caution, and the patient's serum potassium should be monitored frequently.

With Lithium: Increased serum lithium levels and symptoms of lithium toxicity have been reported in patients receiving ACE inhibitors during therapy with lithium. These drugs should be coadministered with caution, and frequent monitoring of serum lithium levels is recommended. If a diuretic is also used, the risk of lithium toxicity may be increased.

Other: Neither ALTACE nor its metabolites have been found to interact with food, digoxin, or antacid.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No evidence of a tumorigenic effect was found when ramipril was given by gavage to rats (up to 500 mg/kg/day for 24 months) or to mice (up to 1,000 mg/kg/day for 18 months). Dosages greatly in excess of those recommended for humans produced hypertrophy of the renal juxtaglomerular apparatus in mice, rats, dogs, and monkeys. No mutagenic activity was detected in the Ames test in bacteria, the micronucleus test in mice, unscheduled DNA synthesis in a human cell line, or a forward gene-mutation assay in a Chinese hamster ovary cell line. Several metabolites and degradation products of ramipril were also negative in the Ames test. A study in rats with dosages as great as 500 mg/kg/day did not produce adverse effects on fertility.

Pregnancy: **Pregnancy Categories C (first trimester) and D (second and third trimesters): See WARNINGS: Fetal/neonatal morbidity and mortality.**

Nursing Mothers: Ingestion of a single 10 mg oral dose of ALTACE resulted in undetectable amounts of ramipril and its metabolites in breast milk. However, because multiple doses may produce low milk concentrations that are not predictable from single doses, ALTACE should not be administered to nursing mothers.

Geriatric Use: Of the total number of patients who received ramipril in US clinical studies of ALTACE 11.0% were 65 and over while 0.2% were 75 and over. No overall differences in effectiveness or safety were observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

One pharmacokinetic study conducted in hospitalized elderly patients indicated that peak ramiprilat levels and area under the plasma concentration-time curve (AUC) for ramiprilat are higher in older patients.

Pediatric Use: Safety and effectiveness in children has not been established.

ADVERSE REACTIONS: ALTACE has been evaluated for safety in over 4,000 patients with hypertension; of these, 1,230 patients were studied in US controlled trials, and 1,107 were studied in foreign controlled trials. Almost 700 of these patients were treated for at least one year. The overall incidence of reported adverse events was similar in ALTACE and placebo patients. The most frequent clinical side effects (possibly or probably related to study drug) reported by patients receiving ALTACE in US placebo-controlled trials were: headache (5.4%), "dizziness" (2.2%) and fatigue or asthenia (2.0%), but only the last was more common in ALTACE patients than in patients given placebo. Generally, the side effects were mild and transient, and there was no relation to total dosage within the range of 1.25 to 20 mg. Discontinuation of therapy because of a side effect was required in approximately 3% of US patients treated with ALTACE. The most common reasons for discontinuation were: cough (1.0%), "dizziness" (0.5%), and impotence (0.4%).

The side effects considered possibly or probably related to study drug that occurred in US placebo-controlled trials in more than 1% of patients treated with ALTACE are shown below:

PATIENTS IN US PLACEBO-CONTROLLED STUDIES

	Altace (N = 651)		Placebo (N = 286)	
	n	%	n	%
Headache	35	5.4	17	5.9
"Dizziness"	14	2.2	9	3.1
Asthenia (Fatigue)	13	2.0	2	0.7
Nausea/Vomiting	7	1.1	3	1.0

In placebo-controlled trials, there was also an excess of upper respiratory infection and flu syndrome in the ramipril group. As these studies were carried out before the relationship of cough to ACE inhibitors was recognized, some of these events may represent ramipril-induced cough. In a later 1-year study, increased cough was seen in almost 12% of ramipril patients, with about 4% of these patients requiring discontinuation of treatment. Other adverse experiences reported in controlled clinical trials (in less than 1% of ramipril patients), or rarer events seen in postmarketing experience, include the following. (In some, a causal relationship to drug use is uncertain.)

Cardiovascular: Symptomatic hypotension (reported in 0.5% of patients in US trials) (see PRECAUTIONS and WARNINGS), syncope (not reported in US trials), angina pectoris, arrhythmia, chest pain, palpitations, myocardial infarction, and cerebrovascular events.

Renal: Some hypertensive patients with no apparent pre-existing renal disease have developed minor, usually transient, increases in blood urea nitrogen and serum creatinine when taking ALTACE, particularly when ALTACE was given concomitantly with a diuretic. (See WARNINGS.)

Angioneurotic Edema: Angioneurotic edema has been reported in 0.3% of patients in US clinical trials. (See WARNINGS.)

Cough: A tickling, dry, persistent, nonproductive cough has been reported with the use of ACE inhibitors. Approximately 1% of patients treated with ALTACE have required discontinuation because of cough. The cough disappears shortly after discontinuation of treatment. (See PRECAUTIONS.)

Gastrointestinal: Abdominal pain (sometimes with enzyme changes suggesting pancreatitis), anorexia, constipation, diarrhea, dry mouth, dyspepsia, dysphagia, gastroenteritis, nausea, increased salivation, taste disturbance, and vomiting.

Dermatologic: Apparent hypersensitivity reactions (manifested by dermatitis, pruritus, or rash, with or without fever), photosensitivity, and purpura.

Neurologic and Psychiatric: Anxiety, amnesia, convulsions, depression, hearing loss, insomnia, nervousness, neuralgia, neuropathy, paresthesia, somnolence, tinnitus, tremor, vertigo, and vision disturbances.

Fetal/Neonatal Morbidity and Mortality: See WARNINGS: Fetal/neonatal morbidity and mortality.

Other: arthralgia, arthritis, dyspnea, edema, epistaxis, impotence, increased sweating, malaise, myalgia, and weight gain.

Clinical Laboratory Test Findings: *Creatinine and Blood Urea Nitrogen:* Increases in creatinine levels occurred in 1.2% of patients receiving ALTACE alone, and in 1.5% of patients receiving ALTACE and a diuretic. Increases in blood urea nitrogen levels occurred in 0.5% of patients receiving ALTACE alone and in 3% of patients receiving ALTACE with a diuretic. None of these increases required discontinuation of treatment. Increases in these laboratory values are more likely to occur in patients with renal insufficiency or those pretreated with a diuretic and, based on experience with other ACE inhibitors, would be expected to be especially likely in patients with renal artery stenosis. (See PRECAUTIONS and WARNINGS.)

Since ramipril decreases aldosterone secretion, elevation of serum potassium can occur. Potassium supplements and potassium-sparing diuretics should be given with caution, and the patient's serum potassium should be monitored frequently. (See PRECAUTIONS and WARNINGS.)

Hemoglobin and Hematocrit: Decreases in hemoglobin or hematocrit (a low value and a decrease of 5 g/dl or 5% respectively) were rare, occurring in 0.4% of patients receiving ALTACE alone and in 1.5% of patients receiving ALTACE plus a diuretic. No US patients discontinued treatment because of decreases in hemoglobin or hematocrit.

Other (causal relationships unknown): Clinically important changes in standard laboratory tests were rarely associated with ALTACE administration. Elevations of liver enzymes, serum bilirubin, uric acid, and blood glucose have been reported, as have scattered incidents of leukopenia, eosinophilia, and proteinuria. In US trials, less than 0.2% of patients discontinued treatment for laboratory abnormalities; all of these were cases of proteinuria or abnormal liver-function tests.

OVERDOSAGE: Human overdoses of ramipril have not been reported, but the most common manifestation of human ramipril overdosage is likely to be hypotension. Because the hypotensive effect of ramipril is achieved through vasodilation and effective hypovolemia, it is reasonable to treat ramipril overdose by infusion of normal saline solution.

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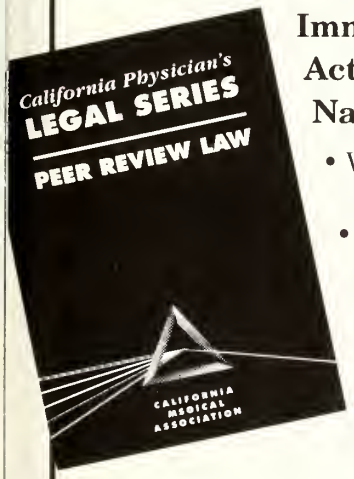

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SCIENTIFIC SESSION

Friday, July 30, 1993

7:00 am	TECHNICAL EXHIBITS OPEN CONTINENTAL BREAKFAST
7:15 am	WELCOME—Joe Daglen, MD, IMA President
7:30-8:30 am	SCUBA DIVING INJURIES Ken Kizer, MD
8:30-9:30 am	RURAL HEALTH ISSUES AND THE CLINTON ADMINISTRATION David A. Kindig, MD, PhD
9:30 am	RECESS TO VIEW EXHIBITS
10:00-11:00 am	ANIMAL ENCOUNTERS Ken Kizer, MD
11:00-noon	TICK-BORNE DISEASES Douglas Gentile, MD
12:00 lunch-1:30	JOIN AUXILIARY RECOGNIZING DOMESTIC VIOLEN Susan Hadley
1:30-2:30 pm	TAKING CHILDREN INTO THE WILDERNESS Barbra Kennedy, MD, and Douglas Gentile, MD
2:30-3:30 pm	MUSHROOM INGESTION DISEASE Jim Blackman, MD

Saturday, July 31, 1993

10:00 am	HEALTH CARE REFORM—THE OREGON PLAN John Kitzhaber, MD, Former Senator from Oregon

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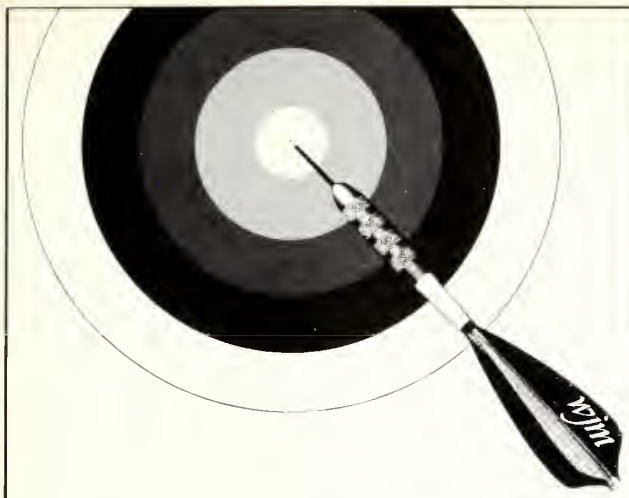

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References:

1. A. Morales et al., New England Journal of Medicine: 1221. November 12, 1981.
2. Goodman, Gilman — The Pharmacological basis of Therapeutics 6th ed., p. 176-188. McMillan December Rev. 1/85.
3. Weekly Urological Clinical Letter, 27:2, July 4, 1983.
4. A. Morales et al., The Journal of Urology 128: 45-47, 1982.

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Brochures, course information, and registration forms are available from the contact person or organization.

July 18-23—**29th Annual Internal Medicine Program.** U of Colo at YMCA of the Rockies, Estes Park. Sun-Fri. Contact: U of Colo.

July 21-25—**34th Annual Scientific Meeting of Colorado Academy of Family Physicians.** CAFP and the Commission on Family Medicine at the Silvertree Hotel and Snowmass Resort, Snowmass. Thurs-Sat. Contact: Randi J. Wathen, Colo Academy of Family Physicians, (303) 696-6655 or FAX (303) 696-7224.

July 25-30—**Physicians and Their Families.** The Menninger Clinic at Grande Butte Hotel, Crested Butte. Sun-Fri. Contact: Jayne Roberts, Box 829, Topeka, KS 66601. (800) 288-7377.

July 26-30—**Breast Imaging and Intervention.** U of Colo at the Broadmoor Hotel, Colorado Springs. Mon-Fri. Contact: U of Colo.

July 26-30—**20th Annual Renal Disease Program.** U of Colo at Given Institute, Aspen. Mon-Fri. Contact: U of Colo.

July 30-August 1—**2nd Annual Medical Ethics Conference.** U of Colo at Aspen. Fri-Sun. Contact: Phyllis Schroeder, U of Colo.

August 2-6—**17th Annual Dynamic Psychotherapy Program.** U of Colo at Given Institute, Aspen. Mon-Fri. Contact: Phyllis Schroeder, U of Colo.

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August 16-17—**Pediatric Nursing Traineeship Program.** Children's Hospital, Denver. Mon-Tues. Contact: Outreach Office, (303) 861-6188.

August 16-19—**Respiratory Therapy Traineeship Program.** Children's Hospital, Denver. Mon-Thurs. Contact: Jeff Griebel, (303) 861-6668.

August 19-21—**3rd Annual Musculoskeletal Infection Society Meeting.** U of Colo at Snowmass Village. Thurs-Sat. Contact: U of Colo.

August 23-28—**18th Annual Primary Musculoskeletal Care Program.** U of Colo at The Village, Breckenridge. Mon-Sat. Contact: Phyllis Schroeder, U of Colo.

September 9-12—**Women in Medicine Third Annual Conference: Inventing Our Future.** Rose Medical Center at Westin Hotel, Vail. Thurs-Sun. Contact: Women in Medicine Conference, Rose Medical Center, (303) 770-2220.

September 20-21—**Pediatric Nursing Traineeship Program.** Children's Hospital, Denver, Mon-Tues. Contact: Outreach Office, (303) 861-6668.

September 21-22, 28-29—**Comprehensive Perinatal Nursing Course.** Children's Hospital at University Hospital, Denver. Tues-Wed. Contact: Trish Beachy, (303) 270-8376.

September 23-25—**The Penrose Cancer Conference: Neoplastic Diseases of the Breast and Ovary.** The Penrose-St Francis Healthcare System at the Broadmoor Hotel, Colorado Springs. Thurs-Sat. Contact: Deborah Hood, Penrose-St Francis Health Care System, PO Box 7021, Colorado Springs 80933-9939. (719) 630-5716.

October 14-16—**Rural Perinatal Traineeship Program.** Children's Hospital, Denver. Thurs-Sat. Contact: Outreach Office, (303) 861-6668.

November 5-6—**16th Annual Perinatal Conference.** Children's Hospital of Denver at Laramie, Wyoming. Fri-Sat. Contact: Conference Office, (303) 861-6946 or (800) 225-0010.

November 11-13—**Rural Perinatal Traineeship Program.** Children's Hospital, Denver. Thurs-Sat. Contact: Outreach Office, (303) 861-6668.

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July 29-31—**Idaho Medical Association Annual Meeting.** Sun Valley. Thurs-Sat. Contact: IMA, 305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888.

NEW MEXICO

Information, requests for accreditation, and items to be listed should be sent to the chair of the CME Committee, New Mexico Medical Society, 7770 Jefferson, Suite 400, Albuquerque, NM 87109, at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 828-0237.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

September 10-11—**New Mexico Chapter, American College of Surgeons Annual Meeting.** Holiday Inn Pyramid, Albuquerque. Fri-Sat. Contact: Bonnie Smith, 7770 Jefferson NE, #400, Albuquerque 87109. (505) 269-5883 or (505) 828-0237.

October 1-2—**John N. Wilson, MD, Lectureship in Cardiology: Cardiology '93.** Albuquerque Hilton Hotel. Fri-Sat. Contact: Mary Boning, PO Box 26666, Albuquerque 87125-6666. (505) 841-1225.

October 2-3—**Pediatric Sports Medicine and Fitness.** Inn of the Mountain Gods, Mescalero/Ruidoso. Sat-Sun. Contact: Richard Rolston, MD, 4808 McMahon Blvd NW, #16, Albuquerque 87114. (505) 898-7898.

October 16—**New Mexico Orthopaedic Association Annual Meeting: Sports Medicine.** Inn at Loretto, Santa Fe. Sat. Contact: Elsa Hall, 7770 Jefferson NE, #400, Albuquerque 87109. (505) 828-0237.

CONTACT INFORMATION

UNM SOM—University of New Mexico School of Medicine, Office of CME, PO Box 713, Albuquerque 87131. (505) 277-3942.

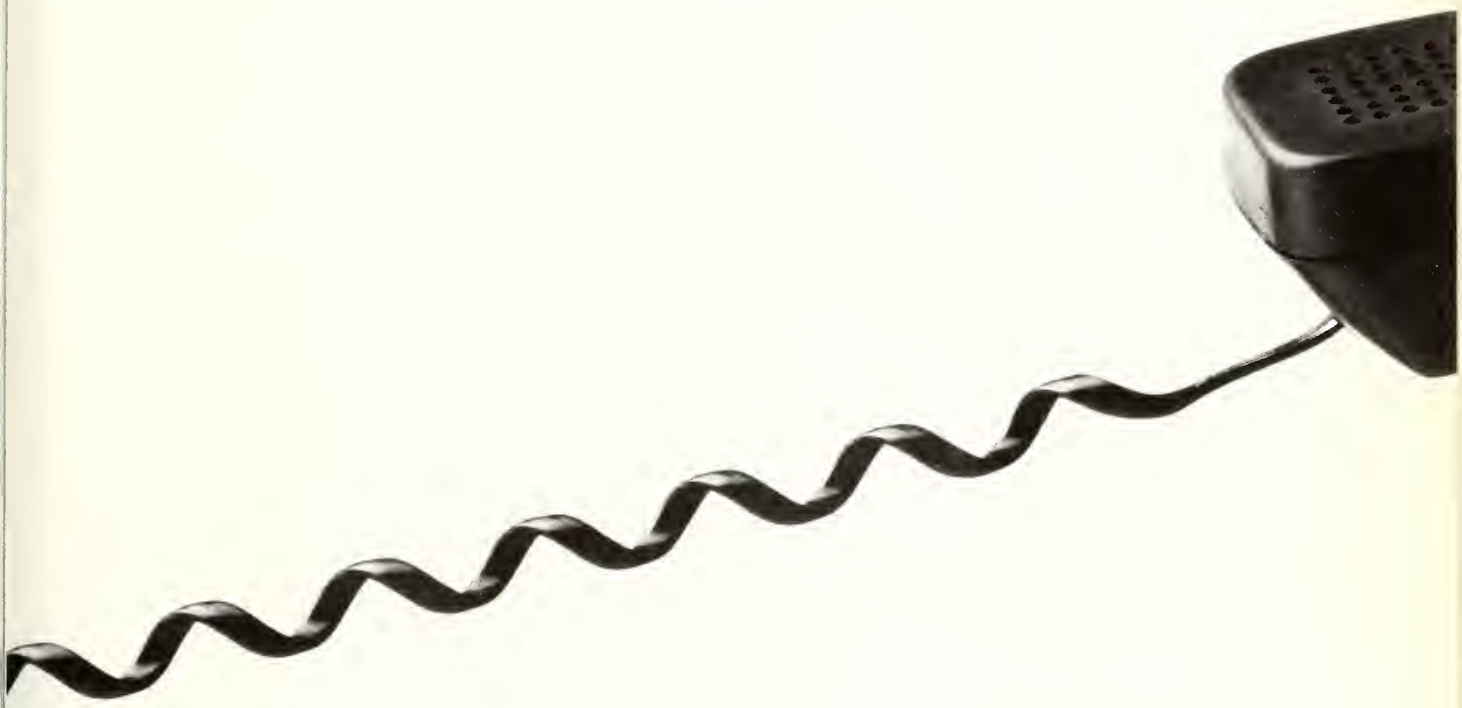
UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. Accredited institutions wishing to list AMA Category 1 CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, UT 84102; or phone (801) 355-5290. For information on CME accreditation, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution.

(Continued on Page 32)

UCLA's medical knowledge can be summed up in one line.



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★ Affiliated Clinical Investigation Societies: the Western Association of Physicians; the Western Society for Clinical Investigation; the Western Section, American Federation for Clinical Research; the Western Society for Pediatric Research; the Western Region, Society for Investigative Dermatology.

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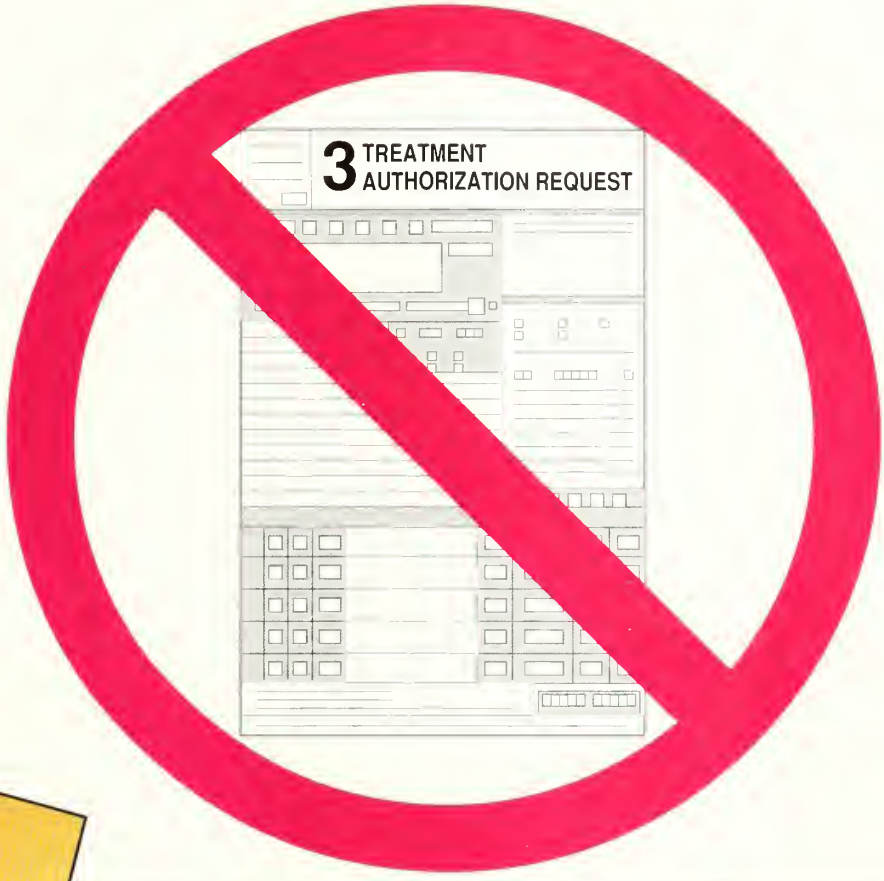
Effective 7/1/93, Lotensin is 1 of only 3 ACE inhibitors approved for use without a TAR*



Lotensin billing codes

5	5-mg tablets	CP 3138 B	20	20-mg tablets	CP 3138 F
10	10-mg tablets	CP 3138 D	40	40-mg tablets	CP 3138 J

Lotensin®

benazepril HCl

* Exception: If a patient has been on "continuing care" with a drug that has been deleted from the *Medi-Cal List of Contract Drugs*, he or she may continue to receive that drug without prior authorization. See *Medi-Cal Pharmacy Bulletin No. 315*.

Please see complete Prescribing Information on following page.

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Lotensin®

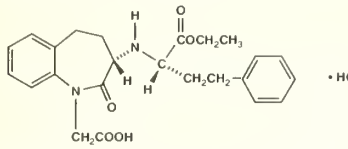
benazepril hydrochloride
Tablets

Prescribing Information

Use in Pregnancy
When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, Lotensin should be discontinued as soon as possible. See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

DESCRIPTION

Benazepril hydrochloride is a white to off-white crystalline powder, soluble (>100 mg/mL) in water, in ethanol, and in methanol. Benazepril's chemical name is 3-[[1-(ethoxy-carbonyl)-3-phenyl-(1S)-propyl]amino]-2,3,4,5-tetrahydro-2-oxo-1*H*-1-(3S)-benzazepine-1-acetic acid monohydrochloride; its structural formula is:



Its empirical formula is $C_{24}H_{28}N_2O_5$•HCl, and its molecular weight is 460.96.

Benazeprilat, the active metabolite of benazepril, is a non-sulfhydryl angiotensin-converting enzyme inhibitor. Benazepril is converted to benazeprilat by hepatic cleavage of the ester group.

Lotensin is supplied as tablets containing 5 mg, 10 mg, 20 mg, and 40 mg of benazepril for oral administration. The inactive ingredients are cellulose compounds, colloidal silicon dioxide, crospovidone, hydrogenated castor oil (5-mg, 10-mg, and 20-mg tablets), iron oxides, lactose, magnesium stearate (40-mg tablets), polysorbate 80, propylene glycol (5-mg and 40-mg tablets), starch, talc, and titanium dioxide.

CLINICAL PHARMACOLOGY

Mechanism of Action

Benazepril and benazeprilat inhibit angiotensin-converting enzyme (ACE) in human subjects and animals. ACE is a peptidyl dipeptidase that catalyzes the conversion of angiotensin I to the vasoconstrictor substance, angiotensin II. Angiotensin II also stimulates aldosterone secretion by the adrenal cortex.

Inhibition of ACE results in decreased plasma angiotensin II, which leads to decreased vasopressor activity and to decreased aldosterone secretion. The latter decrease may result in a small increase of serum potassium. Hypertensive patients treated with Lotensin alone for up to 52 weeks had elevations of serum potassium of up to 0.2 mEq/L. Similar patients treated with Lotensin and hydrochlorothiazide for up to 24 weeks had no consistent changes in their serum potassium (see PRECAUTIONS).

Removal of angiotensin II negative feedback on renin secretion leads to increased plasma renin activity. In animal studies, benazepril had no inhibitory effect on the vasopressor response to angiotensin II and did not interfere with the hemodynamic effects of the autonomic neurotransmitters acetylcholine, epinephrine, and norepinephrine.

ACE is identical to kininase, an enzyme that degrades bradykinin. Whether increased levels of bradykinin, a potent vasodepressor peptide, play a role in the therapeutic effects of Lotensin remains to be elucidated.

While the mechanism through which benazepril lowers blood pressure is believed to be primarily suppression of the renin-angiotensin-aldosterone system, benazepril has an antihypertensive effect even in patients with low-renin hypertension. In particular, Lotensin was antihypertensive in all races studied, although it was somewhat less effective in blacks than in nonblacks.

Pharmacokinetics and Metabolism

Following oral administration of Lotensin, peak plasma concentrations of benazepril are reached within 0.5-1.0 hours. The extent of absorption is at least 37% as determined by urinary recovery and is not significantly influenced by the presence of food in the GI tract.

Cleavage of the ester group (primarily in the liver) converts benazepril to its active metabolite, benazeprilat. Peak plasma concentrations of benazeprilat are reached 1-2 hours after drug intake in the fasting state and 2-4 hours after drug intake in the nonfasting state. The serum protein binding of benazepril is about 96.7% and that of benazeprilat about 95.3%, as measured by equilibrium dialysis; on the basis of in vitro studies, the degree of protein binding should be unaffected by age, hepatic dysfunction, or concentration (over the concentration range of 0.24-23.6 μmol/L).

Benazepril is almost completely metabolized to benazeprilat, which has much greater ACE inhibitory activity than benazepril, and to the glucuronide conjugates of benazepril and benazeprilat. Only trace amounts of an administered dose of Lotensin can be recovered in the urine as unchanged benazepril, while about 20% of the dose is excreted as benazeprilat, 4% as benazepril glucuronide, and 8% as benazeprilat glucuronide.

The kinetics of benazepril are approximately dose-proportional within the dosage range of 10-80 mg.

The effective half-life of accumulation of benazeprilat following multiple dosing of benazepril hydrochloride is 10-11 hours. Thus, steady-state concentrations of benazeprilat should be reached after 2 or 3 doses of benazepril hydrochloride given once daily.

The kinetics did not change, and there was no significant accumulation during chronic administration (28 days) of once-daily doses between 5 mg and 20 mg. Accumulation ratios based on AUC and urinary recovery of benazeprilat were 1.19 and 1.27, respectively.

When dialysis was started two hours after ingestion of 10 mg of benazepril, approximately 6% of benazeprilat was removed in 4 hours of dialysis. The parent compound, benazepril, was not detected in the dialysate.

The disposition of benazepril and benazeprilat in patients with mild-to-moderate renal insufficiency (creatinine clearance >30 mL/min) is similar to that in patients with normal renal function. In patients with creatinine clearance ≤30 mL/min, peak benazeprilat levels and the initial (alpha phase) half-life increase, and time to steady state may be delayed (see DOSAGE AND ADMINISTRATION).

Benazepril and benazeprilat are cleared predominantly by renal excretion in healthy subjects with normal renal function. Nonrenal (i.e., biliary) excretion accounts for approximately 11-12% of benazeprilat excretion in healthy subjects. In patients with renal failure, biliary clearance may compensate to an extent for deficient renal clearance.

In patients with hepatic dysfunction due to cirrhosis, levels of benazeprilat are essentially unaltered. The pharmacokinetics of benazepril and benazeprilat do not appear to be influenced by age.

In studies in rats given ^{14}C-benazepril, benazepril and its metabolites crossed the blood-brain barrier only to an extremely low extent. Multiple doses of benazepril did not result in accumulation in any tissue except the lung, where, as with other ACE inhibitors in similar studies, there was a slight increase in concentration due to slow elimination in that organ.

Some placental passage occurred when the drug was administered to pregnant rats.

Pharmacodynamics

Single and multiple doses of 10 mg or more of Lotensin cause inhibition of plasma ACE activity by at least 80-90% for at least 24 hours after dosing. Pressor responses to exogenous angiotensin I were inhibited by 60-90% (up to 4 hours post-dose) at the10 mg dose.

Administration of Lotensin to patients with mild-to-moderate hypertension results in a reduction of both supine and standing blood pressure to about the same extent with no compensatory tachycardia. Symptomatic postural hypotension is infrequent, although it can occur in patients who are salt- and/or volume-depleted (see WARNINGS).

In single-dose studies, Lotensin lowered blood pressure within 1 hour, with peak reductions achieved 2-4 hours after dosing. The antihypertensive effect of a single dose persisted for 24 hours. In multiple-dose studies, once-daily doses of 20-80 mg decreased seated pressure (systolic/diastolic) 24 hours after dosing by about 6-12 /4-7 mmHg. The trough values represent reductions of about 50% of that seen at peak.

Four dose-response studies using once-daily dosing were conducted in 470 mild-to-moderate hypertensive patients not using diuretics. The minimal effective once-daily dose of Lotensin was 10 mg, but further falls in blood pressure, especially at morning trough, were seen with higher doses in the studied dosing range (10-80 mg). In studies comparing the same daily dose of Lotensin given as a single morning dose or as a twice-daily dose, blood pressure reductions at the time of morning trough blood levels were greater with the divided regimen.

During chronic therapy, the maximum reduction in blood pressure with any dose is generally achieved after 1-2 weeks. The antihypertensive effects of Lotensin have continued during therapy for at least two years. Abrupt withdrawal of Lotensin has not been associated with a rapid increase in blood pressure.

In patients with mild-to-moderate hypertension, Lotensin 10-20 mg was similar in effectiveness to captopril, hydrochlorothiazide, nifedipine SR, and propranolol.

The antihypertensive effects of Lotensin were not appreciably different in patients receiving high- or low-sodium diets.

In hemodynamic studies in dogs, blood pressure reduction was accompanied by a reduction in peripheral arterial resistance, with an increase in cardiac output and renal blood flow and little or no change in heart rate. In normal human volunteers, single doses of benazepril caused an increase in renal blood flow but had no effect on glomerular filtration rate.

Use of Lotensin in combination with thiazide diuretics gives a blood-pressure-lowering effect greater than that seen with either agent alone. By blocking the renin-angiotensin-aldosterone axis, administration of Lotensin tends to reduce the potassium loss associated with the diuretic.

INDICATIONS AND USAGE

Lotensin is indicated for the treatment of hypertension. It may be used alone or in combination with thiazide diuretics.

In using Lotensin, consideration should be given to the fact that another angiotensin-converting enzyme inhibitor, captopril, has caused agranulocytosis, particularly in patients with renal impairment or collagen-vascular disease. Available data are insufficient to show that Lotensin does not have a similar risk (see WARNINGS).

CONTRAINDICATIONS

Lotensin is contraindicated in patients who are hypersensitive to this product or to any other ACE inhibitor.

WARNINGS

Angioedema

Angioedema of the face, extremities, lips, tongue, glottis, and larynx has been reported in patients treated with angiotensin-converting enzyme inhibitors. In U.S. clinical trials, symptoms consistent with angioedema were seen in none of the subjects who received placebo and in about 0.5% of the subjects who received Lotensin. Angioedema associated with laryngeal edema can be fatal. If laryngeal stridor or angioedema of the face, tongue, or glottis occurs, treatment with Lotensin should be discontinued and appropriate therapy instituted immediately. **Where there is involvement of the tongue, glottis, or larynx, likely to cause airway obstruction, appropriate therapy, e.g., subcutaneous epinephrine injection 1:1000 (0.3 mL to 0.5 mL) should be promptly administered (see ADVERSE REACTIONS).**

Hypotension

Lotensin can cause symptomatic hypotension. Like other ACE inhibitors, benazepril has been only rarely associated with hypotension in uncomplicated hypertensive patients. Symptomatic hypotension is most likely to occur in patients who have been volume- and/or salt-depleted as a result of prolonged diuretic therapy, dietary salt restriction, dialysis, diarrhea, or vomiting. Volume- and/or salt-depletion should be corrected before initiating therapy with Lotensin.

In patients with congestive heart failure, with or without associated renal insufficiency, ACE inhibitor therapy may cause excessive hypotension, which may be associated with oliguria or azotemia and, rarely, with acute renal failure and death. In such patients, Lotensin therapy should be started under close medical supervision; they should be followed closely for the first 2 weeks of treatment and whenever the dose of benazepril or diuretic is increased.

If hypotension occurs, the patient should be placed in a supine position, and, if necessary, treated with intravenous infusion of physiological saline. Lotensin treatment usually can be continued following restoration of blood pressure and volume.

Neutropenia/Agranulocytosis

Another angiotensin-converting enzyme inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression, rarely in uncomplicated patients, but more frequently in patients with renal impairment, especially if they also have a collagen-vascular disease such as systemic lupus erythematosus or scleroderma. Available data from clinical trials of benazepril are insufficient to show that benazepril does not cause agranulocytosis at similar rates. Monitoring of white blood cell counts should be considered in patients with collagen-vascular disease, especially if the disease is associated with impaired renal function.

Fetal/Neonatal Morbidity and Mortality

ACE inhibitors can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature. When pregnancy is detected, ACE inhibitors should be discontinued as soon as possible.

The use of ACE inhibitors during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to the ACE inhibitor exposure.

These adverse effects do not appear to have resulted from intrauterine ACE inhibitor exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to ACE inhibitors only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should make every effort to discontinue the use of benazepril as soon as possible.

Rarely (probably less often than once in every thousand pregnancies), no alternative to ACE inhibitors will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intraamniotic environment.

If oligohydramnios is observed, benazepril should be discontinued unless it is considered life-saving for the mother. Contraction stress testing (CST), a nonstress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of *in utero* exposure to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function. Benazepril, which crosses the placenta, can theoretically be removed from the neonatal circulation by these means; there are occasional reports of benefit from these maneuvers with another ACE inhibitor, but experience is limited.

No teratogenic effects of Lotensin were seen in studies of pregnant rats, mice, and rabbits. On a mg/m^2 basis, the doses used in these studies were 60 times (in rats), 9 times (in mice), and more than 0.8 times (in rabbits) the maximum recommended human dose (assuming a 50 kg woman). On a mg/kg basis these multiples are 300 times (in rats), 90 times (in mice) and more than 3 times (in rabbits) the maximum recommended human dose.

PRECAUTIONS

General

Impaired Renal Function: As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe congestive heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with angiotensin-converting enzyme inhibitors, including Lotensin, may be associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death. In a small study of hypertensive patients with renal artery stenosis in a solitary kidney or bilateral renal artery stenosis, treatment with Lotensin was associated with increases in blood urea nitrogen and serum creatinine; these increases were reversible upon discontinuation of Lotensin or diuretic therapy, or both. When such patients are treated with ACE inhibitors, renal function should be monitored during the first few weeks of therapy. Some hypertensive patients with no apparent preexisting renal vascular disease have developed increases in blood urea nitrogen and serum creatinine, usually minor and transient, especially when Lotensin has been given concomitantly with a diuretic. This is more likely to occur in patients with preexisting renal impairment. Dosage reduction of Lotensin and/or discontinuation of the diuretic may be required. **Evaluation of the hypertensive patient should always include assessment of renal function (see DOSAGE AND ADMINISTRATION).**

Hemodialysis Patients: Anaphylactoid reactions have been reported in patients dialyzed with high-flux membranes and treated concomitantly with an ACE inhibitor. In these patients, consideration should be given to using a different type of dialysis membrane or a different class of antihypertensive agent.

Hyperkalemia: In clinical trials, hyperkalemia (serum potassium at least 0.5 mEq/L greater than the upper limit of normal) occurred in approximately 1% of hypertensive patients receiving Lotensin. In most cases, these were isolated values which resolved despite continued therapy. Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with Lotensin (see Drug Interactions).

Cough: Cough has been reported with the use of ACE inhibitors. Characteristically, the cough is nonproductive, persistent, and resolves after discontinuation of therapy. ACE inhibitor-induced cough should be considered as part of the differential diagnosis of cough.

Impaired Liver Function: In patients with hepatic dysfunction due to cirrhosis, levels of benazeprilat are essentially unaltered.

Surgery/Anesthesia: In patients undergoing surgery or during

anesthesia with agents that produce hypotension, benazepril will block the angiotensin II formation that could otherwise occur secondary to compensatory renin release. Hypotension that occurs as a result of this mechanism can be corrected by volume expansion.

Information for Patients

Pregnancy: Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to ACE inhibitors, and they should also be told that these consequences do not appear to have resulted from intrauterine ACE inhibitor exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.

Angioedema: Angioedema, including laryngeal edema, can occur with treatment with ACE inhibitors, especially following the first dose. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, eyes, lips, or tongue, or difficulty in breathing) and to take no more drug until they have consulted with the prescribing physician.

Symptomatic Hypotension: Patients should be cautioned that lightheadedness can occur, especially during the first days of therapy, and it should be reported to the prescribing physician. Patients should be told that if syncope occurs, Lotensin should be discontinued until the prescribing physician has been consulted.

All patients should be cautioned that inadequate fluid intake or excessive perspiration, diarrhea, or vomiting can lead to an excessive fall in blood pressure, with the same consequences of lightheadedness and possible syncope.

Hyperkalemia: Patients should be told not to use potassium supplements or salt substitutes containing potassium without consulting the prescribing physician.

Neutropenia: Patients should be told to promptly report any indication of infection (e.g., sore throat, fever), which could be a sign of neutropenia.

Drug Interactions

Diuretics: Patients on diuretics, especially those in whom diuretic therapy was recently instituted, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with Lotensin. The possibility of hypotensive effects with Lotensin can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with Lotensin. If this is not possible, the starting dose should be reduced (see DOSAGE AND ADMINISTRATION).

Potassium Supplements and Potassium-Sparing Diuretics: Lotensin can attenuate potassium loss caused by thiazide diuretics. Potassium-sparing diuretics (spironolactone, amiloride, triamterene, and others) or potassium supplements can increase the risk of hyperkalemia. Therefore, if concomitant use of such agents is indicated, they should be given with caution, and the patient's serum potassium should be monitored frequently.

Oral Anticoagulants: Interaction studies with warfarin and acenocoumarol failed to identify any clinically important effects on the serum concentrations or clinical effects of these anticoagulants.

Lithium: Increased serum lithium levels and symptoms of lithium toxicity have been reported in patients receiving ACE inhibitors during therapy with lithium. These drugs should be coadministered with caution, and frequent monitoring of serum lithium levels is recommended. If a diuretic is also used, the risk of lithium toxicity may be increased.

Other: No clinically important pharmacokinetic interactions occurred when Lotensin was administered concomitantly with hydrochlorothiazide, chlorthalidone, furosemide, digoxin, propranolol, atenolol, naproxen, or cimetidine.

Lotensin has been used concomitantly with beta-adrenergic-blocking agents, calcium-channel-blocking agents, diuretics, digoxin, and hydralazine, without evidence of clinically important adverse interactions. Benazepril, like other ACE inhibitors, has had less than additive effects with beta-adrenergic blockers, presumably because both drugs lower blood pressure by inhibiting parts of the renin-angiotensin system.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No evidence of carcinogenicity was found when benazepril was administered to rats and mice for up to two years at doses of up to 150 mg/kg/day. When compared on the basis of body weights, this dose is 110 times the maximum recommended human dose. When compared on the basis of body surface areas, this dose is 18 and 9 times (rats and mice, respectively) the maximum recommended human dose (calculations assume a patient weight of 60 kg). No mutagenic activity was detected in the Ames test in bacteria (with or without metabolic activation), in an in vitro test for forward mutations in cultured mammalian cells, or in a nucleus anomaly test. In doses of 50-500 mg/kg/day (6-60 times the maximum recommended human dose based on mg/m^2 comparison and 37-375 times the maximum recommended human dose based on a mg/kg comparison), Lotensin had no adverse effect on the reproductive performance of male and female rats.

Pregnancy Categories C (first trimester) and D (second and third trimesters)

See WARNINGS, Fetal/Neonatal Morbidity and Mortality

Nursing Mothers

Minimal amounts of unchanged benazepril and of benazeprilat are excreted into the breast milk of lactating women treated with benazepril. A newborn child ingesting entirely breast milk would receive less than 0.1% of the mg/kg maternal dose of benazepril and benazeprilat.

Geriatric Use

Of the total number of patients who received benazepril in U.S. clinical studies of Lotensin, 18% were 65 or older while 2% were 75 or older. No overall differences in effectiveness or safety were observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Pediatric Use

Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Lotensin has been evaluated for safety in over 6000 patients with hypertension; over 700 of these patients were treated for at least one year. The overall incidence of reported adverse events was comparable in Lotensin and placebo patients.

The reported side effects were generally mild and transient, and there was no relation between side effects and age, duration of therapy, or total dosage within the range of 2 to 80 mg. Discontinuation of therapy because of a side effect was required in approximately 5% of U.S. patients treated with Lotensin and in 3% of patients treated with placebo.

The most common reasons for discontinuation were headache (0.6%) and cough (0.5%), (see PRECAUTIONS, Cough).

The side effects considered possibly or probably related to study drug that occurred in U.S. placebo-controlled trials in more than 1% of patients treated with Lotensin are shown below.

PATIENTS IN U.S. PLACEBO-CONTROLLED STUDIES

	LOTENSIN (N=964)		PLACEBO (N=496)	
	N	%	N	%
Headache	60	6.2	21	4.2
Dizziness	35	3.6	12	2.4
Fatigue	23	2.4	11	2.2
Somnolence	15	1.6	2	0.4
Postural Dizziness	14	1.5	1	0.2
Nausea	13	1.3	5	1.0
Cough	12	1.2	5	1.0

Other adverse experiences reported in controlled clinical trials (in less than 1% of benazepril patients), and rarer events seen in postmarketing experience, include the following (in some, a causal relationship to drug use is uncertain):

Cardiovascular: Symptomatic hypotension was seen in 0.3% of patients, postural hypotension in 0.4%, and syncope in 0.1%; these reactions led to discontinuation of therapy in 4 patients who had received benazepril monotherapy and in 9 patients who had received benazepril with hydrochlorothiazide (see PRECAUTIONS and WARNINGS). Other reports included angina pectoris, palpitations, and peripheral edema.

Renal: Of hypertensive patients with no apparent preexisting renal disease, about 2% have sustained increases in serum creatinine to at least 150% of their baseline values while receiving Lotensin, but most of these increases have disappeared despite continuing treatment. A much smaller fraction of these patients (less than 0.1%) developed simultaneous (usually transient) increases in blood urea nitrogen and serum creatinine.

Fetal/Neonatal Morbidity and Mortality: See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

Angioedema: Angioedema has been reported in patients receiving ACE inhibitors. During clinical trials in hypertensive patients with benazepril, 0.5% of patients experienced edema of the lips or face without other manifestations of angioedema. Angioedema associated with laryngeal edema and/or shock may be fatal. If angioedema of the face, extremities, lips, tongue, or glottis and/or larynx occurs, treatment with Lotensin should be discontinued and appropriate therapy instituted immediately (see WARNINGS).

Gastrointestinal: Constipation, gastritis, vomiting, and melena.

Dermatologic: Apparent hypersensitivity reactions (manifested by dermatitis, pruritus, or rash), photosensitivity, and flushing.

Neurologic and Psychiatric: Anxiety, decreased libido, hypertonia, insomnia, nervousness, and paresthesia.

Other: Arthralgia, arthritis, asthenia, asthma, bronchitis, dyspnea, impotence, infection, myalgia, sinusitis, sweating, and urinary tract infection.

Clinical Laboratory Test Findings

Creatinine and Blood Urea Nitrogen: Of hypertensive patients with no apparent preexisting renal disease, about 2% have sustained increases in serum creatinine to at least 150% of their baseline values while receiving Lotensin, but most of these increases have disappeared despite continuing treatment. A much smaller fraction of these patients (less than 0.1%) developed simultaneous (usually transient) increases in blood urea nitrogen and serum creatinine. None of these increases required discontinuation of treatment. Increases in these laboratory values are more likely to occur in patients with renal insufficiency or those pretreated with a diuretic and, based on experience with other ACE inhibitors, would be expected to be especially likely in patients with renal artery stenosis (see PRECAUTIONS, General).

Potassium: Since benazepril decreases aldosterone secretion, elevation of serum potassium can occur. Potassium supplements and potassium-sparing diuretics should be given with caution, and the patient's serum potassium should be monitored frequently (see PRECAUTIONS).

Hemoglobin: Decreases in hemoglobin (a low value and a decrease of 5 g/dL) were rare, occurring in only 1 of 2014 patients receiving Lotensin alone and in 1 of 1357 patients receiving Lotensin plus a diuretic. No U.S. patients discontinued treatment because of decreases in hemoglobin.

Other (causal relationships unknown): Clinically important changes in standard laboratory tests were rarely associated with Lotensin administration. Elevations of liver enzymes, serum bilirubin, uric acid, and blood glucose have been reported, as have scattered incidents of hyponatremia, electrocardiographic changes, leukopenia, eosinophilia, and proteinuria. In U.S. trials, less than 0.5% of patients discontinued treatment because of laboratory abnormalities.

OVERDOSAGE

Single oral doses of 3 g/kg benazepril were associated with significant lethality in mice. Rats, however, tolerated single oral doses of up to 6 g/kg. Reduced activity was seen at 1 g/kg in mice and at 5 g/kg in rats. Human overdoses of benazepril have not been reported, but the most common manifestation of human benazepril overdosage is likely to be hypotension.

Laboratory determinations of serum levels of benazepril and its metabolites are not widely available, and such determinations have, in any event, no established role in the management of benazepril overdose.

No data are available to suggest physiological maneuvers (e.g., maneuvers to change the pH of the urine) that might accelerate elimination of benazepril and its metabolites. Benazepril is only slightly dialyzable, but dialysis might be considered in overdosed patients with severely impaired renal function (see PRECAUTIONS, Hemodialysis Patients).

Angiotensin II could presumably serve as a specific antagonist-antidote in the setting of benazepril overdose, but angiotensin II is essentially unavailable outside of scattered research facilities. Because the hypotensive effect of benazepril is achieved through vasodilation and effective hypovolemia, it is reasonable to treat benazepril overdose by infusion of normal saline solution.

DOSAGE AND ADMINISTRATION

The recommended initial dose for patients not receiving a diuretic is 10 mg once-a-day. The usual maintenance dosage range is 20-40 mg per day administered as a single dose or in two equally divided doses. A dose of 80 mg gives an increased response, but experience with this dose is limited. The divided regimen was more effective in controlling trough (pre-dosing) blood pressure than the same dose given as a once-daily regimen. Dosage adjustment should be based on measurement of peak (2-6 hours after dosing) and trough responses. If a once-daily regimen does not give adequate trough response an increase in dosage or divided administration should be considered. If blood pressure is not controlled with Lotensin alone, a diuretic can be added.

Total daily doses above 80 mg have not been evaluated.

Concomitant administration of Lotensin with potassium supplements, potassium salt substitutes, or potassium-sparing diuretics can lead to increases of serum potassium (see PRECAUTIONS).

In patients who are currently being treated with a diuretic, symptomatic hypotension occasionally can occur following the initial dose of Lotensin. To reduce the likelihood of hypotension, the diuretic should, if possible, be discontinued two to three days prior to beginning therapy with Lotensin (see WARNINGS). Then, if blood pressure is not controlled with Lotensin alone, diuretic therapy should be resumed.

If the diuretic cannot be discontinued, an initial dose of 5 mg Lotensin should be used to avoid excessive hypotension.

Dosage Adjustment in Renal Impairment

For patients with a creatinine clearance <30 mL/min/1.73 m^2 (serum creatinine >3 mg/dL), the recommended initial dose is 5 mg Lotensin once daily. Dosage may be titrated upward until blood pressure is controlled or to a maximum total daily dose of 40 mg (see PRECAUTIONS, Hemodialysis Patients).

HOW SUPPLIED

Lotensin is available in tablets of 5 mg, 10 mg, 20 mg, and 40 mg, packaged with a desiccant in bottles of 100 tablets. Lotensin is also supplied in blister packages (1 tablet/blister), in Accu-Pak® Unit Dose boxes containing 10 strips of 10 blisters each.

Each tablet is imprinted with LOTENSIN on one side and the tablet strength ("5", "10", "20", or "40") on the other. Samples, when available, are identified by the word *SAMPLE* on each tablet.

The National Drug Codes for the various packages are.

Dose	Tablet Color	Bottle of 100	Accu-Pak® of 100
5 mg	light yellow	NDC 0083-0059-30	NDC 0083-0059-32
10 mg	dark yellow	NDC 0083-0063-30	NDC 0083-0063-32
20 mg	tan	NDC 0083-0079-30	NDC 0083-0079-32
40 mg	dark rose	NDC 0083-0094-30	NDC 0083-0094-32

Storage: Do not store above 86° F (30° C). Protect from moisture.

Dispense in tight container (USP).

Printed in U.S.A. C92-44 (Rev. 10/92)

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ABSTRACTS JULY 1993

(Moore WS: Carotid endarterectomy for prevention of stroke. West J Med 1993; 159: 37-43)

Carotid endarterectomy, a frequently performed operation, has been used as a strategy for preventing stroke in patients with carotid bifurcation disease. The safety and efficacy of the operation were recently challenged by a number of sources. Three major responses to this challenge were to retrospectively review the natural history of carotid bifurcation disease compared with the immediate and long-term results of carotid endarterectomy, to initiate 6 prospective randomized trials to determine the efficacy of carotid endarterectomy for a variety of indications, and to develop appropriateness initiatives and guidelines for using this surgical procedure by organizations concerned with health care policy. I review the current status of these 3 areas of endeavor. In those areas where studies are complete, carotid endarterectomy has been shown to be highly effective in reducing stroke risk. Risk reduction has ranged from 66% to 80% compared with medical management. Based on these sources and findings, I present a list of indications for the operation for surgeons who are able to do the operation safely and within the guidelines established by the Stroke Council of the American Heart Association.

CAROTID ENDARTERECTOMY STROKE PREVENTION
CAROTID BIFURCATION DISEASE

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CONTINUING MEDICAL EDUCATION

(Continued from Page 24)

July 29-31—**Summer Shakespearean Meeting.** Cedar City. Thurs-Sat. Contact: UOS.

September 22-25—**Utah Medical Association Annual Meeting.** University Park Hotel, Salt Lake City. Wed-Sat. Contact: UMA, 540 E Fifth South, Salt Lake City 84102. (801) 355-7477.

MEDICAL GRAND ROUNDS

Weekly— Internal Medicine Grand Rounds, Psychiatry Grand Rounds, OB/GYN Grand Rounds, Pediatric Grand Rounds. Contact: UUSM, Office of CME, (801) 581-8664.

SPONSORS OF COURSES—ABBREVIATIONS

CH: Castleview Hospital, 300 N Hospital Dr, Price 84501. (801) 637-4800.

CS: Charter Summit Hospital, 175 W 7200 South, Midvale 84047. (801) 561-8181.

DM: Dixie Medical Center, 544 S 400 East, St George 84770. (801) 634-4000.

ETS: Emergency Training Services, 777 N 390 East, American Fork 84003. (801) 763-3555.

FHP: FHP of Utah, 35 W Broadway, Salt Lake City 84101. (801) 355-1234.

ITS: Intermountain Thoracic Society, 1616 S 11th East, Salt Lake City 84105. (801) 484-4456.

LDSH: LDS Hospital, 8th Ave and "C" St, Salt Lake City 84143. (801) 321-1100.

LRH: Logan Regional Hospital, 1400 N 5th East, Logan 84321. (801) 752-2050.

MVH: Mountain View Hospital, 1000 E Highway 6, Payson 84651. (801) 465-9201.

OSS: Ogden Surgical-Medical Society, PO Box 9311, Ogden 84409.

PCMC: Primary Children's Medical Center, 100 N Medical Dr, Salt Lake City 84113. (801) 588-2000.

PVH: Pioneer Valley Hospital, 3460 S 4155 West, West Valley City 84120. (801) 968-9061.

UMIA: Utah Medical Insurance Association, 540 E 500 South, Salt Lake City 84102. (801) 531-0375.

UOS: Utah Ophthalmological Society, 540 E 500 South, Salt Lake City 84102. (801) 355-7477.

USH: Utah State Hospital, PO Box 270, Provo 84603-0270. (801) 373-4400.

UUSM: University of Utah School of Medicine, Office of Continuing Medical Education, 50 N Medical Dr, Salt Lake City 84132. (801) 581-8664.

VAMC: Veterans Administration Medical Center, 500 Foothill Dr, Salt Lake City 84148. (801) 582-1565.

WASHINGTON

The listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here, please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121; or phone (206) 441-WSMA.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

July 16—**AIDS Update: A Primary Look.** Renton. Fri. Contact: VMC, (206) 228-3440.

August 2-7—**Summer Seminar in Health Care Ethics.** Seattle. Mon-Sat. Contact: U/W.

August 15-18—**Oncology.** Everett. Sun-Wed. Contact: PNMEII. (206) 258-6322.

August 27-28—**Children's Orthopedic Conference.** Seattle. Fri-Sat. Contact: Children's Hospital, (206) 526-2501.

September 9-12—**Washington State Medical Association Annual Meeting and Scientific Session.** Jantzen Beach, Oregon. Thurs-Sun. Contact: WSMA.

September 10—**Emergency Physicians Scientific Session.** Jantzen Beach. Fri. Contact: WACEP, (206) 441-9762.

September 11—**Ophthalmology Scientific Session.** Jantzen Beach. Sat. Contact: WAEPS, (206) 441-9762.

September 13-17—**21st Annual Advances in Family Practice.** Seattle. Mon-Fri. Contact: U/W.

September 17-18—**Children's Orthopedic Conference.** Seattle. Fri-Sat. Contact: Children's Hospital. (206) 526-2501.

September 22-25—**North Pacific Pediatric Society.** Vancouver, BC. Wed-Sat. Contact: Children's. (206) 258-6322.

September 23—**Domestic Violence.** Everett. Thurs. Contact: PNMEII, (206) 258-6322.

September 24-25—**Diabetes Update.** Seattle. Fri-Sat. Contact: U/W.

September 30-October 1—**Atherosclerosis and Restenosis.** Seattle. Thurs-Fri. Contact: U/W.

October 1—**Pharmacology.** Tacoma. Fri. Contact: Multicare, (206) 522-1221.

October 8-9—**Society for Pediatric Pathology.** Seattle. Wed-Fri. Contact: Children's Hospital, (206) 526-2501.

October 8-9—**Upper Respiratory Infection.** Seattle. Fri-Sat. Contact: U/W.

October 15—**The Walking Wounded—Acute Care Outside the ICU.** Everett. Fri. Contact: PNMEII, (206) 258-6322.

October 22-23—**Adolescent Medicine.** Seattle. Thurs-Fri. Contact: Children's Hospital, (206) 526-2501.

October 23—**Pediatric Endocrinology.** Tacoma. Fri. Contact: Multicare, (206) 522-1221.

October 27—**Perinatology Conference.** Tacoma. Wed. Contact: Multicare, (206) 552-1221.

November 4-5—**Drug Therapy.** Seattle. Thurs-Fri. Contact: U/W.

November 18-19—**Regional Musculoskeletal Conference.** Seattle. Thurs-Fri. Contact: U/W.

November 19—**Advances in Therapeutics for the Clinician.** Renton. Fri. Contact: VMC, (206) 228-3440.

December 2-4—**American College of Physicians.** Seattle. Thurs-Sat. Contact: U/W.

December 9-12—**9th Infectious Disease Conference.** Everett. Tues-Sat. Contact: PNMEII, (206) 258-6322.

December 10-11—**Regional Musculoskeletal Conference.** Seattle. Fri-Sat. Contact: U/W.

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104. (206) 223-5953.

PCMS CME—Contact: Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 223-6898.

WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Suite 900, Seattle, WA 98121. (206) 441-9762.

WYOMING

June 10-12—**Wyoming Medical Society—Annual Meeting.** Jackson Lake Lodge, Moran. Thurs-Sat.

October 29-30—**16th Annual Perinatal Conference.** Children's Hospital of Denver at Laramie. Fri-Sat. Contact: Conference Office, (303) 861-6946 or (800) 225-0010. ◆

CONTINUING MEDICAL EDUCATION CALENDAR

The Southern Medical Association is accredited by the Accreditation Council for Continuing Medical Education to sponsor continuing medical education for physicians.

JULY 26-29, 1993

FOCUS ON THE FEMALE PATIENT
LOCATION: Kiawah Island Resort, Kiawah Island, South Carolina (Near Charleston)
SPECIALTY: Ob/Gyn, Primary Care
CME CREDIT: CAT I-18; AAFP 18 Prescribed; ACOG 19 Cognates; AOA 18 CAT 2A
FEE: SMA Member-$295; Nonmember-$420; Nonphysician-$200

JULY 30-AUGUST 1, 1993

FOCUS ON THE MALE PATIENT
LOCATION: Kiawah Island Resort, Kiawah Island, South Carolina (Near Charleston)
SPECIALTY: Primary Care, Urology
CME CREDIT: CAT I-14; AAFP 13 Prescribed; AOA 14 CAT 2A
FEE: SMA Member-$295; Nonmember-$420; Nonphysician-$200

AUGUST 1993

HOW TO COLLECT FOR CONTROL
LOCATIONS:

August 3	Jacksonville, Florida
August 4	Miami, Florida
August 5	Tallahassee, Florida
August 6	Tampa, Florida
August 10	Mobile, Alabama
August 11	Jackson, Mississippi
August 12	Birmingham, Alabama
August 13	Atlanta, Georgia

FEE: SMA Member or Employee-$135; Nonmember or Employee-$235

AUGUST 5-7, 1993

SOUTHERN ASSOCIATION FOR ONCOLOGY, SIXTH ANNUAL MEETING
LOCATION: Frenchman's Reef, St. Thomas, Virgin Islands
SPECIALTY: Physicians practicing oncology in all disciplines
CME CREDIT: Up to 11 CAT I
FEE: SMA/SAO Member-$400; Nonmember-$525; Nonphysician-$150

AUGUST 12-14, 1993

SOUTHERN ORTHOPAEDIC ASSOCIATION, TENTH ANNUAL MEETING
LOCATION: Vienna, Austria
SPECIALTY: Orthopaedic and Traumatic Surgeons
CME CREDIT: Up to 13 CAT I
FEE: SMA/SOA Member-$450; Nonmember-$525; Nonphysician-$150

AUGUST 27-29, 1993

FAMILY MEDICINE UPDATE
LOCATION: Callaway Gardens, Pine Mountain, Georgia
SPECIALTY: Primary Care, Family Practice
CME CREDIT: CAT I-14, AAFP 14 Prescribed; AOA 14 CAT 2A
FEE: SMA Member-$295; Nonmember-$470

OCTOBER 28-31, 1993

SOUTHERN
MEDICAL
ASSOCIATION'S

87TH ANNUAL SCIENTIFIC ASSEMBLY

LOCATION: New Orleans Convention Center, New Orleans, Louisiana

FEATURES:

- 25 Medical Specialty Section Meetings
- 19 Joint Specialty Section Meetings
- 34 Postgraduate Courses
- 15 Clinical and Scientific Symposia
- 29 Round Table Luncheon Sessions With Featured Experts

and more...

CME CREDIT: AMA CAT I, up to 25 Hours

FEE: SMA Member-$75; Nonmember-$200. Fee waived for Physicians-in-Training

For more information, call Michelle Williamson, Southern Medical Association, 800-423-4992 or 205-945-1840—TODAY!

ABSTRACTS JULY 1993

(Elks ML, Sawyer JW Jr: Misunderstanding in the classification of diabetes mellitus—What's in a name? West J Med 1993; 159:44-49)

To assess whether physicians, residents, medical students, hospital diagnosis coders, and patients properly use the designations insulin-dependent diabetes mellitus (IDDM) and non—insulin-dependent diabetes mellitus (NIDDM) that were established by criteria of the National Diabetes Data Group, we reviewed clinic and hospital records and administered questionnaires. Although essentially all cases of true IDDM were identified as such and most cases of NIDDM not requiring insulin therapy were correctly identified by all groups, patients with NIDDM on insulin therapy were misidentified as having IDDM by 38% of residents in internal medicine clinics and 68% of primary care and surgical subspecialty residents. On a survey, of 22 patients with NIDDM on insulin therapy, 17 (77%) considered themselves to have IDDM. Thus, patients who have NIDDM by the established criteria who are on insulin therapy are commonly mislabeled as having IDDM. We present an approach for dealing with this problem by adapting nomenclature focusing on insulin deficiency and resistance. It would probably also be helpful to separately identify the subset of patients with "insulin-deficient diabetes" who are ketosis-prone. It is important to use immunologic profiling (islet cell antibody testing) and insulin sensitivity or deficiency testing (C-peptide levels).

DIABETES MELLITUS
DIABETES NOMENCLATURE
CLASSIFYING DIABETES
INSULIN-DEPENDENT DIABETES MELLITUS
NON-INSULIN-DEPENDENT DIABETES MELLITUS

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NON-INSULIN-DEPENDENT DIABETES MELLITUS

Three copies of this abstract are provided to help you in filing and cross-referencing research articles.

CEFOBID® (cefoperazone sodium) has maintained in vitro activity over time

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Pseudomonas aeruginosa[2,3]		*Staphylococcus aureus*[2,3]	
1985	1990	1985	1990
91.0%	93.1%	92.0%	91.3%
(n=388)	(n=15,439)	(n=369)	(n=2,554)

From a retrospective, multicenter susceptibility data base; n=number of isolates; percent susceptible calculated with 95% confidence limits.

In vitro activity does not necessarily imply a correlation with *in vivo* results.

- An established record of clinical effectiveness in nosocomial pneumonia,* in complicated UTI,* and for approved indications in the febrile neutropenic patient*[4-8]
- No dosage adjustment required for the renally impaired
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Contraindicated in patients with known allergy to the cephalosporin class of antibiotics

CEFOBID® 1g/2g q12h (cefoperazone sodium) IM/IV

A force against resistance

*Due to susceptible strains of indicated organisms, such as *P aeruginosa*.

References. 1. Horan T, Culver D, Jarvis W, et al. Pathogens causing nosocomial infections: preliminary data from the National Nosocomial Infections Surveillance System. *Antimicrobic Newsletter* 1988;5(9):65-67. **2.** Data available on request from Roerig. **3.** Jenkins SG. Comparative susceptibility patterns of common clinical isolates to cefoperazone: 1981 to 1987. *Am J Med* 1988;85(suppl 1A):52-55. **4.** Mangi RJ, Greco T, Ryan J, Thorton G, Andriole VT. Cefoperazone versus combination antibiotic therapy of hospital acquired pneumonia. *Am J Med* 1988;84:68-74. **5.** Mangi RJ, Ryan J, Berenson C, et al. Cefoperazone versus ceftazidime monotherapy of nosocomial pneumonia. *Am J Med* 1988;85(suppl 1A):44-48. **6.** Mangi R, Peccerillo K, Moleski RJ. Treatment of nosocomial pneumonia. Presented as an educational exhibit at the 47th Annual Meeting of the American Society of Hospital Pharmacists, June 3-7, 1990, Boston, Mass. **7.** Cohen MS, Washton HE, Barranco SF. Multicenter clinical trial of cefoperazone sodium in the United States. *Am J Med* 1984;77:35-41. **8.** Kiehl A, Greenberg RN. Treatment of febrile neutropenic patients: evaluation of antibiotic regimens with or without vancomycin. Presented at the 24th Annual ASHP Midyear Clinical Meeting, December 3-7, 1989, Atlanta, Ga.

Brief Summary

CEFOBID® (cefoperazone sodium) *For Intravenous or Intramuscular Use*

CONTRAINDICATIONS: CEFOBID (cefoperazone sodium) is contraindicated in patients with known allergy to the cephalosporin class of antibiotics. **WARNINGS**: BEFORE THERAPY WITH CEFOBID IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEPHALOSPORINS, PENICILLINS OR OTHER DRUGS. THIS PRODUCT SHOULD BE GIVEN CAUTIOUSLY TO PENICILLIN-SENSITIVE PATIENTS. ANTIBIOTICS SHOULD BE ADMINISTERED WITH CAUTION TO ANY PATIENT WHO HAS DEMONSTRATED SOME FORM OF ALLERGY, PARTICULARLY TO DRUGS. SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE THE USE OF SUBCUTANEOUS EPINEPHRINE AND OTHER EMERGENCY MEASURES.

PSEUDOMEMBRANOUS COLITIS HAS BEEN REPORTED WITH THE USE OF CEPHALOSPORINS (AND OTHER BROAD-SPECTRUM ANTIBIOTICS). THEREFORE, IT IS IMPORTANT TO CONSIDER ITS DIAGNOSIS IN PATIENTS WHO DEVELOP DIARRHEA IN ASSOCIATION WITH ANTIBIOTIC USE. **PRECAUTIONS**: Although transient elevations of the BUN and serum creatinine have been observed, CEFOBID alone does not appear to cause significant nephrotoxicity. However, concomitant administration of aminoglycosides and other cephalosporins has caused nephrotoxicity.

CEFOBID is extensively excreted in bile. The serum half-life of CEFOBID is increased 2-4 fold in patients with hepatic disease and/or biliary obstruction. In general, total daily dosage above 4 g should not be necessary in such patients. If higher dosages are used, serum concentrations should be monitored.

Because renal excretion is no, the main route of elimination of CEFOBID, patients with renal failure require no adjustment in dosage when usual doses are administered. When high doses of CEFOBID are used, concentrations of drug in the serum should be monitored periodically. If evidence of accumulation exists, dosage should be decreased accordingly.

The half-life of CEFOBID is reduced slightly during hemodialysis. Thus, dosing should be scheduled to follow a dialysis period. In patients with both hepatic dysfunction and significant renal disease, CEFOBID dosage should not exceed 1-2 g daily without close monitoring of serum concentrations.

As with other antibiotics, vitamin K deficiency has occurred rarely in patients treated with CEFOBID. Those at risk include patients with a poor nutritional status, malabsorption states (e.g., cystic fibrosis), alcoholism, and patients on prolonged hyperalimentation regimens (administered either intravenously or via a nasogastric tube). Prothrombin time should be monitored in these patients and exogenous vitamin K administered as indicated.

A disulfiram-like reaction characterized by flushing, sweating, headache, and tachycardia has been reported when alcohol (beer, wine) was ingested within 72 hours after CEFOBID (cefoperazone sodium) administration. Patients should be cautioned about the ingestion of alcoholic beverages following the administration of CEFOBID. A similar reaction has been reported with other cephalosporins.

Prolonged use of CEFOBID may result in the overgrowth of nonsusceptible organisms. Careful observation of the patient is essential.

CEFOBID should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis. **Drug Laboratory Test Interactions**: A false-positive reaction for glucose in the urine may occur with Benedict's or Fehling's solution. **Carcinogenesis, Mutagenesis, Impairment of Fertility**: The maximum duration of CEFOBID animal toxicity studies is six months. In none of the *in vivo* or *in vitro* genetic toxicology studies did CEFOBID show any mutagenic potential at either the chromosomal or subchromosomal level. CEFOBID produced no impairment of fertility and had no effects on general reproductive performance or fetal development when administered subcutaneously at daily doses up to 500 to 1000 mg/kg prior to and during mating, and to pregnant female rats during gestation. These doses are 10 to 20 times the estimated usual single clinical dose. Cefoperazone had adverse effects on the testes of prepubertal rats at all doses tested. Subcutaneous administration of 100 mg/kg per day (approximately 1/3 times the average adult human dose) resulted in reduced germinal cell population and vacuolation of Sertoli cell cytoplasm. The severity of lesions was dose dependent in the 100 to 1000 mg/kg per day range; the low dose caused a minor decrease in spermatocytes. This effect has not been observed in adult rats. Histologically the lesions were reversible at all but the highest dosage levels. However, these studies did not evaluate subsequent development of reproductive function in the rats. The relationship of these findings to humans is unknown. **Usage in Pregnancy; Pregnancy Category B**: Reproduction studies have been performed in mice, rats, and monkeys at doses up to 10 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to CEFOBID. There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. **Usage in Nursing Mothers**: Only low concentrations of CEFOBID are excreted in human milk. Although CEFOBID passes poorly into breast milk of nursing mothers, caution should be exercised when CEFOBID is administered to a nursing woman. **Pediatric Use**: Safety and effectiveness in children have not been established. For information concerning testicular changes in prepubertal rats see Carcinogenesis, Mutagenesis, Impairment of Fertility. **ADVERSE REACTIONS**: In clinical studies the following adverse effects were observed and were considered to be related to CEFOBID (cefoperazone sodium) therapy or uncertain etiology. **Hypersensitivity**: As with all cephalosporins, hypersensitivity manifested by skin reactions (1 patient in 45), drug fever (1 in 260), or a change in Coombs' test (1 in 60) has been reported. These reactions are more likely to occur in patients with a history of allergies, particularly to penicillin. **Hematology**: As with other beta-lactam antibiotics, reversible neutropenia may occur with prolonged administration. Slight decreases in neutrophil count (1 patient in 50) have been reported. Decreased hemoglobins (1 in 20) or hematocrits (1 in 20) have been reported, which is consistent with published literature on other cephalosporins. Transient eosinophilia has occurred in 1 patient in 10. **Hepatic**: Of 1285 patients treated with cefoperazone in clinical trials one patient with a history of liver disease developed significantly elevated liver function enzymes during CEFOBID therapy. Clinical signs and symptoms or nonspecific hepatitis accompanied these increases. After CEFOBID therapy was discontinued, the patient's enzymes returned to pretreatment levels and the symptomatology resolved. As with other antibiotics that achieve high bile levels, mild transient elevations of liver function enzymes have been observed in 5-10% of the patients receiving CEFOBID therapy. The relevance of these findings, which were not accompanied by overt signs or symptoms of hepatic dysfunction, has not been established. **Gastrointestinal**: Diarrhea or loose stools has been reported in 1 in 30 patients. Most of these experiences have been mild or moderate in severity and self-limiting in nature. In all cases, these symptoms responded to symptomatic therapy or ceased when cefoperazone therapy was stopped. Nausea and vomiting have been reported rarely.

Symptoms of pseudomembranous colitis can appear during or for several weeks subsequent to antibiotic therapy (see WARNINGS). **Renal Function Tests**: Transient elevations of the BUN (1 in 16) and serum creatinine (1 in 48) have been noted. **Local Reactions**: CEFOBID is well tolerated following intramuscular administration. Occasionally, transient pain (1 in 140) may follow administration by this route. When CEFOBID is administered by intravenous infusion some patients may develop phlebitis (1 in 120) at the infusion site.

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Articles

Carotid Endarterectomy for Prevention of Stroke

WESLEY S. MOORE, MD, *Los Angeles, California*

Presented at the meeting of the California Academy of Medicine, San Francisco, California, September 26, 1992.

Carotid endarterectomy, a frequently performed operation, has been used as a strategy for preventing stroke in patients with carotid bifurcation disease. The safety and efficacy of the operation were recently challenged by a number of sources. Three major responses to this challenge were to retrospectively review the natural history of carotid bifurcation disease compared with the immediate and long-term results of carotid endarterectomy, to initiate 6 prospective randomized trials to determine the efficacy of carotid endarterectomy for a variety of indications, and to develop appropriateness initiatives and guidelines for using this surgical procedure by organizations concerned with health care policy. I review the current status of these 3 areas of endeavor. In those areas where studies are complete, carotid endarterectomy has been shown to be highly effective in reducing stroke risk. Risk reduction has ranged from 66% to 80% compared with medical management. Based on these sources and findings, I present a list of indications for the operation for surgeons who are able to do the operation safely and within the guidelines established by the Stroke Council of the American Heart Association.

(Moore WS: Carotid endarterectomy for prevention of stroke. West J Med 1993; 159:37-43)

Stroke continues to be the third leading cause of death in the United States each year. It also represents a major cause of morbidity and contributes heavily to health care costs. The current annual incidence of stroke is about 195 per 100,000 people, and the incidence increases with increasing age. Thus, in men aged 55 to 64, the incidence is 300 per 100,000 and increases dramatically in the age group 75 to 84, with an incidence of 1,440 per 100,000.[1] Of the patients who survive the initial stroke, about two thirds will be disabled to some degree. Half of the survivors will live for about five years, and a third of the survivors require prolonged inpatient rehabilitation.[2]

The recognition of the correlation between carotid bifurcation disease and ischemic hemispheric stroke from a thromboembolic event was long in coming. Since the first reported operation on the carotid bifurcation in 1954, however, there has been a rapid rise in the use of carotid endarterectomy as a strategy for stroke prevention. The annual number of operations rose from 17,000 in 1971 to about 100,000 in 1984.[3] The enthusiasm for the surgical procedure continued to grow until 1984 when a pivotal issue of the journal *Stroke* appeared (volume 15, number 6) that contained a collection of articles questioning the efficacy and use of carotid endarterectomy.[4-7] This collection was prefaced by an editorial entitled "Carotid Endarterectomy—An Expression of Concern," written by three eminent neurologists from Canada, the United States, and the United Kingdom.[8] This challenge attracted much attention by scientists and the lay media, causing sufficient doubt to be cast on the efficacy of this surgical procedure and resulting in a major cutback in its use over the next few years. In addition, and as a consequence of this heated debate, three major endeavors were initiated. These included a series of reports documenting the natural history of carotid bifurcation disease compared with retrospective reviews of surgical series, looking at both initial and long-term outcomes; a series of prospective randomized trials that were begun or further supported; and various interest groups getting together to develop appropriateness initiatives or practice guidelines for the use of carotid endarterectomy. In this report I shall discuss and analyze the results of these three major courses of action and shall summarize the current indications for carotid endarterectomy based on the best available data, including prospective randomized trials and the analysis of results by expert panels.*

Natural History Studies and Retrospective Reviews

The early reported series of carotid endarterectomy dealt primarily with the surgical morbidity and mortality associated with the operation. Over time, the incidence of death within 30 days and of perioperative stroke contin-

*See also the editorial "Carotid Endarterectomy—The Big Picture," by J. F. Toole, MD, on pages 90-91 of this issue.

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ABBREVIATIONS USED IN TEXT

AMCC = Academic Medical Center Consortium
CASANOVA = Carotid Artery Surgery Asymptomatic Narrowing Operation Versus Aspirin
NASCET = North American Symptomatic Carotid Endarterectomy Trial
TIA = transient ischemic attack
VA = [Department of] Veterans Affairs

ued to decline in centers of excellence. Community-based studies showed an alarming incidence of perioperative death and stroke, however, when the overall experience was surveyed in contrast to that of single institutions.[6,9] These findings were taken into consideration by those who were challenging the efficacy of carotid endarterectomy and its widespread use. There were little data available at that time to determine the long-term results in patients who had undergone carotid endarterectomy. Therefore, many institutions began a concerted effort to look at not only the perioperative results but also the late consequences in patients treated by carotid endarterectomy with regard to the subsequent incidence of stroke as well as survival. Obviously, if there was shortened survival among patients with carotid bifurcation disease, the widespread application of carotid endarterectomy as a preventive procedure may well not have an important effect for the population at risk. Finally, although there were early natural history studies of the incidence of stroke in various patient subgroups, the subgroup analysis was poorly defined. For example, many articles dealt with the incidence of stroke associated with transient ischemic attacks (TIAs). Yet, the character of the TIAs was inevitably heterogeneous, and the nature of the underlying lesion with respect to the percentage of stenosis or plaque composition was not defined.

Retrospective reviews primarily divided patient groups by their symptomatic status and compared results in patients without treatment, in those with the use of antiplatelet drugs, and in those with carotid endarterectomy.

Territorial Transient Cerebral Ischemia

Natural history studies suggest that patients with monocular or hemispheric TIAs have a risk of stroke that ranges from 10% to 30% within one year of the beginning of symptoms and continues at the rate of 6% per year thereafter, yielding an overall stroke risk of 35% to 50% within five years of the onset of symptoms.[10-15] The use of antiplatelet drugs, particularly aspirin, has been extensively studied. Aspirin therapy will lower the risk of stroke in patients with hemispheric and monocular TIAs, but the benefit is small. Meta-analysis of all the aspirin trials suggests that the overall benefit of aspirin use is to lower the stroke rate by about 15%.[16] This effectively means that if the incidence of stroke in a particular subgroup was 10% in one year, a 15% risk reduction would lower it to 8.5%.

Carotid endarterectomy for patients having hemispheric or monocular TIAs will carry a variable operative risk ranging from 3% to as high as 18% for neurologic morbidity and mortality.[9,17-23] The American Heart Association has recommended that for carotid endarterectomy to be effective in patients who have had TIAs, the combined neurologic morbidity and mortality following the operation must not exceed 5%.[24] Many centers of excellence are currently achieving rates considerably less than this. After successful carotid endarterectomy, the annual stroke rate drops to a range of 1% to 2%.[20,25-30] This is in marked contrast to that in patients who receive medical management alone and represents a 67% stroke risk reduction.

Previous Stroke With Minimal Residual Deficit

Patients who have had a previous hemispheric stroke remain at risk for a subsequent stroke at the rate of 5% to 20% per year, with the average five-year recurrence rate being 50%.[31-34] Carotid endarterectomy for patients who have had a previous stroke and have made a good recovery carries a higher risk than that for patients who have not yet had a stroke. The Stroke Council of the American Heart Association has recommended that the operative risk for patients who have had a previous stroke and have made a good recovery should not exceed 7%.[24] Once again, centers of excellence have been able to achieve morbidity and mortality rates of less than 5%, and many are reporting rates of 3%. After successful carotid endarterectomy, the recurrent stroke rate is reduced to an event rate of 2% per year.[20,28,29,35-37] In contrast, patients who are treated medically have recurrent stroke rates ranging from 9% to 16% per year.[31-34] Therefore, at the end of five years, an operation appears to reduce the stroke risk by at least 66% compared with medical management alone.

Asymptomatic Carotid Stenosis

Patients who have asymptomatic stenoses with 75% or more reduction in the diameter of the carotid bulb have been shown to have neurologic event rates (TIA and stroke) of 18% in one year.[38] The event rate for stroke alone is about 5% in one series but may be lower. Another series has shown that the risk of combined events of TIA, stroke, or occlusion of the internal carotid artery in patients with more than 80% diameter-reducing stenosis is 46% within 12 months of diagnosis.[39] Internal carotid occlusion, even though it may occur without symptoms initially, carries a risk of subsequent stroke of 5% to 10% per year.[40,41] This is of concern because once the internal carotid artery is occluded, the opportunity to restore or preserve patency has been lost because the internal carotid artery is an unbranched vessel and thrombus will propagate intracranially.

Carotid endarterectomy for patients with asymptomatic stenoses carries the lowest risk of any category. The Stroke Council of the American Heart Association recommends that this operation be performed with a risk of less than 3%.[24] Our recently reported series carried a combined neurologic morbidity and mortality of 1.4%.[42] Following successful carotid endarterectomy, the risk of subsequent stroke in the distribution of the treated artery

averages 0.3% per year in cumulative series.[43-45] The incidence of stroke in our series was 0% in the distribution of the surgically treated artery with a mean follow-up of 54 months.[42]

Miscellaneous Categories

A number of other subsets of patients include those who present with global ischemic symptoms, acute stroke, and evolving stroke. The numbers of these patients are small, and the reports at best are anecdotal. Therefore, decisions of whether or not to offer the operation for this category of patient must be tailored for each patient and cannot, at the present time, be definitively answered from the available literature.

Prospective Randomized Trials

Although retrospective data appear to confirm the efficacy of carotid endarterectomy when compared with medical management alone, there are many criticisms and potential pitfalls associated with retrospective analyses and historic controls. For this reason, prospective randomized trials were initiated to evaluate the effect of adding carotid endarterectomy to medical management and risk factor control to determine definitively whether or not carotid endarterectomy lowered the stroke risk in specific subsets of patients with atherosclerotic disease of the carotid bifurcation. There are currently six prospective randomized trials in various stages of progress or completion. Three of these examine asymptomatic patients with hemodynamically notable stenoses of the carotid bifurcation,[46-49] and the other three examine patients with symptomatic disease.[50-52] It is anticipated that when these studies are complete and the data are analyzed, definitive answers will be established with regard to the efficacy of carotid endarterectomy and hence the indication for its application.

Asymptomatic Patients

Veterans Affairs (VA) Cooperative Study. The VA initiated the first of the prospective randomized trials for asymptomatic patients. This study was begun in 1980 and involved 11 VA Medical Centers.[46,47] Patients with 50% or greater diameter-reducing stenoses and with no symptoms in the distribution of the study artery were prospectively randomly allocated to one of two treatment groups; the control group received aspirin antiplatelet therapy and risk factor reduction, and the experimental group received aspirin antiplatelet therapy, risk factor reduction, and carotid endarterectomy. A total of 444 patients were entered into the study and were observed for five to seven years. The study was designed to test the hypothesis that carotid endarterectomy plus aspirin antiplatelet therapy would be more effective than antiplatelet therapy alone in reducing the incidence of neurologic events, including TIA and stroke. The results of the study clearly supported the hypothesis and demonstrated that the combined incidence of ipsilateral neurologic events in the surgical group at the end of follow-up was 8.0%, in contrast to an event rate of 20.6% in the medical group ($P < .001$). Because the study was designed to look at the end points of both TIA and stroke, the sample size was adjusted for the combined end points and was not large enough to provide statistical power for showing a difference in the analysis of stroke alone. Nonetheless, the ipsilateral stroke rate in the surgical group was 4.7% compared with 9.4% in the medical group ($P < .06$). When perioperative mortality was added to stroke morbidity, the difference between the two groups with respect to stroke failed to reach statistical significance. As a consequence, the results of this trial will continue to be controversial. Those who favor the use of carotid endarterectomy in asymptomatic patients as an important method of prophylaxis will cite the positive findings of the trial, and those who are opposed to its use will emphasize the lack of definitive data when analyzing stroke alone as an end point.

Carotid Artery Surgery Asymptomatic Narrowing Operation Versus Aspirin (CASANOVA). The CASANOVA study, a European trial, was designed to determine the efficacy of the operation on asymptomatic patients.[49] A total of 410 patients with stenoses ranging from 50% to less than 90% were randomly allocated to one of two groups. The experimental group received carotid endarterectomy plus antiplatelet drugs (n = 206), and the control group was to have received antiplatelet drugs alone (n = 204). In a careful review of the report, several flaws of design and statistical analysis were revealed that seriously compromise the value of the study. First, patients with stenoses of 90% or greater, perhaps the highest risk group, were excluded from entry into the study and were operated on preferentially. Therefore, the opportunity to evaluate this group and to add them to the analysis was lost. In addition, there were a number of problems associated with the control group. A large percentage of the patients in the control group actually received an operation, but in an "intent-to-treat" design analysis, the result was not attributed to an operation but to medical management. Patients in the control group receiving an operation included those with bilateral carotid stenoses in whom the stenosis of greater compromise was treated with carotid endarterectomy and the lesser lesion was observed. Furthermore, if a patient was allocated to medical management and during the course of study the lesion progressed to a stenosis of 90% or greater, the patient was switched to the group having carotid endarterectomy. If bilateral carotid stenosis developed in a patient in the control group during the course of follow-up, carotid endarterectomy was done on one lesion if it exceeded a 50% in diameter reduction. Finally, patients who were allocated to the medical group were switched to the group having carotid endarterectomy if symptoms of transient cerebral ischemia developed. While all of these indications for an operation would appear to be reasonable, none of the events for which a patient allocated to the medical group was converted to surgical treatment were charged as an end point or considered a failure of therapy for purposes of statistical analysis. The result was that of the 206 who were randomly assigned to medical treatment, 118 (57%) actually underwent carotid endarterectomy but were analyzed as if

they were treated with medical management alone. Not surprisingly, there were no statistically significant differences between the surgical group and the group receiving "medical management." The authors of the study erroneously concluded that carotid endarterectomy was not efficacious in asymptomatic patients in preventing stroke. A more appropriate conclusion might have been that selective carotid endarterectomy offered to patients with stenoses in excess of 90%, patients with bilateral carotid stenoses, or patients in whom symptoms developed was as effective as the routine application of carotid endarterectomy in all patients.

Asymptomatic Carotid Artery Stenosis Study. The Asymptomatic Carotid Artery Stenosis Study is a prospective randomized trial sponsored by the National Institutes of Health and involving 34 centers in North America.[48] When completed, it will be the largest and possibly the most definitive trial of carotid endarterectomy in patients with asymptomatic carotid stenosis. The study is testing the hypothesis that carotid endarterectomy, when added to aspirin therapy plus risk factor modification, will reduce the incidence of TIA and cerebral infarction in patients with hemodynamically notable carotid stenosis when compared with patients treated with aspirin plus risk factor modification alone. The design of the trial includes randomly allocating 1,500 patients into the two treatment arms. A five-year follow-up will be included.

The randomizing of patients began in the spring of 1988. To date, about 1,300 patients have been randomly allocated, and it is anticipated that the allocation will be completed in the winter of 1993. The hope is that with this large sample size, a definitive answer will be forthcoming with respect not only to the combined end points of TIA and stroke but also to stroke alone.

Symptomatic Patients

North American Symptomatic Carotid Endarterectomy Trial (NASCET). The NASCET trial, a large, ambitious, randomized study involving several centers in the United States and Canada, was intended to enroll 3,000 patients who were having TIAs or stroke within 120 days of the event, provided that they had angiographic evidence of an appropriate carotid bulb stenosis ranging from 30% to 99%. In the randomizing process, patients were stratified into two groups based on the degree of stenosis: 30% to 69% and 70% to 99%. These were randomly allocated to a control group that received the best available medical management and an experimental group that included the best available medical management plus carotid endarterectomy.

In February 1991 a "clinical alert" was issued by the National Institutes of Health that patients who were in the 70%- to 99%-stenosis group did dramatically better with carotid endarterectomy than those who were treated with the best medical management alone. Therefore, this portion of the study was stopped, and the rest of the patients who were in the control group were advised to undergo carotid endarterectomy. When compared with medical therapy, surgical therapy reduced the risk of stroke by 71% and the risk of death by 58%. The conclusion was that carotid endarterectomy was highly beneficial for symptomatic patients with high-grade stenoses. At the time of that review, a dramatic difference did not exist for the subgroup of patients with stenoses in the range of 30% to 69%, and that portion of the study continues to this date.[50]

European Carotid Surgery Trial. The European Carotid Surgery Trial, involving several centers, randomly allocated 2,518 patients over a ten-year period.[51] The study patients were stratified into three groups depending on the degree of stenosis: mild (0% to 29%), moderate (30% to 69%), and severe (70% to 99%). At about the same time as the clinical alert for the NASCET trial was announced, the European study reported similar results in the high-grade stenosis category. They also noted that patients with mild lesions appeared to derive no benefit from the operation compared with medical management alone. They, like the NASCET investigators, are continuing to randomly allocate patients with moderate stenoses in the range of 30% to 69%. In patients with severe stenosis, surgical therapy reduced the risk of subsequent ipsilateral stroke by more than 80%.

Veterans Affairs Symptomatic Trial. The VA study of symptomatic patients with high-grade stenoses was at an early stage when the results of the NASCET study and the European trial were reported. Because it would have been unethical to continue to randomly allocate patients to less effective therapy, the study was stopped. The opportunity was then presented to evaluate the results in 189 patients who were randomly allocated to carotid endarterectomy and best medical management (n = 91) and a control group of patients who were treated with best medical management alone (n = 98). After a mean follow-up interval of only 11.9 months, there was a significant benefit to patients who received carotid endarterectomy compared with that to the control group. Thus, the results of this study further corroborate the data presented by the NASCET trial and by the European study. The VA study also added an additional dimension, and that had to do with patients who were having crescendo TIAs. This trial showed that those patients were at particularly high risk of stroke in the control group and did statistically significantly better when treated with carotid endarterectomy.[52]

Appropriateness Initiatives and Practice Guidelines

Because of the controversial nature of carotid endarterectomy and the conflicting data that had previously been published, several organizations have taken the initiative to review the available data and publish their reports concerning appropriate indications for carotid endarterectomy and practice guidelines. I shall highlight three initiatives and include the Rand-Academic Medical Center Consortium (AMCC) initiative, the publication of a report by the Ad Hoc Committee of the Joint Council of the Society for Vascular Surgery and the North American Chapter of the International Society for Cardiovascular

Surgery, and an ongoing effort by the Office of Quality Assurance by the American Medical Association.

Rand-Academic Medical Center Consortium Appropriateness Initiative

The Rand Corporation, a think tank located in Santa Monica, California, reviews critical issues in many disciplines. Health care is one such discipline, and the utilization of various procedures, including carotid endarterectomy, has been a major focus of this organization. The AMCC consists of a group of ten academic medical centers that work together on areas of mutual interest. In 1990 these two organizations combined efforts to evaluate the appropriateness of the use of several procedures including carotid endarterectomy. The Rand Corporation assumed the task of developing appropriateness and necessity criteria for the use of carotid endarterectomy, and the AMCC assumed the responsibility of using these criteria in a self-audit of the practice patterns in their respective medical centers. Following the audit, key people from each of the academic medical centers were invited to participate in a conference to critique the Rand ratings and to review the results of the combined audit of the hospitals within the AMCC and of their individual hospitals. The objective of this effort was to develop appropriateness criteria, tested in academic medical centers, that could then be made available to professional societies for the development of practice guidelines.

The Rand Corporation works in the following manner. The literature is reviewed, and opinions from local experts and designated members of specific medical specialty societies are solicited. Following this, an initial set of possible indications for carotid endarterectomy is developed. A panel of physicians with specific skills in the area of cerebrovascular disease is selected from nominations by medical specialty societies with interest in cerebrovascular disease.

The final panel included representation from the disciplines of neurology, vascular surgery, neurologic surgery, cardiology, and neuroradiology. Each panel member was given a copy of the literature review and a list of the possible indications for carotid endarterectomy and was asked to make an appropriateness rating for the operation based on a nine-point scale: A score of 9.0 would indicate that the operation was highly appropriate, and a score of 1.0 would indicate that the operation was clearly inappropriate. The initial ratings were performed individually in confidence. The group was then convened, discussions were carried out, and a second set of ratings was obtained. The results were then collated, and a median score in the range of 7 to 9 indicated an appropriate indication for carotid endarterectomy, 4 to 6 designated uncertain appropriateness (or split opinion), and 1 to 3 represented an inappropriate indication for operation. The Rand panel went a step further and carried out a survey of necessity ratings. In this instance, an indication for carotid endarterectomy was not only appropriate but represented the best form of treatment and therefore would be considered necessary. As such, failure to offer carotid endarterectomy would be considered inappropriate. The initial results of the literature survey, the appropriateness ratings, and the necessity ratings have been published by the Rand Corporation.[53] Subsequent publications from the joint Rand-AMCC effort are forthcoming.

Recommendations of the Joint Council of the Society for Vascular Surgery and the International Society for Cardiovascular Surgery

The Joint Council of the Society for Vascular Surgery and the International Society for Cardiovascular Surgery identified the need to develop guidelines for applying carotid endarterectomy. An ad hoc committee was convened, and at an initial meeting it was determined that the committee structure should be extended to involve other disciplines. The final committee therefore included three vascular surgeons, two neurologists, and a neurologic surgeon. This group thoroughly searched the literature, concentrating primarily on recent publications that reviewed the natural history of carotid artery disease, the contemporary risks of the operation, and the immediate and long-term results in patients treated with carotid endarterectomy. They also examined the results of prospective randomized trials where data were available. This committee published a report that reviewed the various presenting features of patients with carotid artery disease and commented on the circumstance under which carotid endarterectomy was the best treatment and those conditions that were best managed medically.[54]

American Medical Association Effort

The Office of Quality Assurance of the American Medical Association looked at several surgical procedures and, to address practice guidelines, mounted an effort to reach a consensus concerning their application. A committee was developed consisting of members representing the various specialty organizations that had a specific interest in the procedures being reviewed, including carotid endarterectomy. A subcommittee was asked to address the issue of carotid endarterectomy and did this by reviewing the Rand-AMCC report and comparing it with the Joint Council's publication. This effort is still going on and will include a comparison of ratings and a final suggested list of indications for carotid endarterectomy. The initial review and comparison of the two documents yielded a high degree of concordance concerning indications for carotid endarterectomy (Matchar DB, Huesgen CT, Moore WS, "Indications for Carotid Endarterectomy: A Comparison of Ratings by a Multidisciplinary Expert Panel With Recommendations from the Joint Council of the Society for Vascular Surgery and the International Society for Cardiovascular Surgery [North American Chapter]," unpublished data, March 1993). With the passage of time and the accumulation of data, both retrospective and prospective, the risks, benefits, and hence indications for the application of the operation are apparently becoming better defined and more universally accepted. Because there was excellent concordance between these two efforts, and until the recommendations are actually pub-

TABLE 1.—*Current Indications for Carotid Endarterectomy*

Patients	Source of Recommendation: Retrospective Data Analysis	Rand Panel	Joint Council*	Randomized Trials
Symptomatic				
Single focal TIA (>70% stenosis)	Yes	Yes	Yes	Yes
Multiple focal TIAs with				
>70% Stenosis	Yes	Yes	Yes	Yes
>50% Stenosis with ulceration	Yes	Yes	Yes	NA
50% to 69% Stenosis†	Yes	Yes	Yes	NA
30% to 49% Stenosis†	Yes	Yes	Yes	NA
<30% Stenosis with or without ulcer†	Yes	Yes	Yes	No
Previous stroke (mild), ipsilateral				
>70% Stenosis	Yes	Yes	Yes	Yes
>50% With large ulcer	Yes	Yes	Yes	NA
30% to 69% with and without ulcer	Yes	Yes	Yes	NA
Evolving stroke				
>70% Stenosis	Yes	Yes	Yes	NA
Global symptoms				
>70% Carotid stenosis with uncorrectable vertebrobasilar disease	Yes	Yes	Yes	NA
Asymptomatic				
>70% Stenosis with contralateral occlusion or high-grade stenosis	Yes	Yes	Yes	NA
>70% Unilateral stenosis	Yes	No	Yes	NA
Large ulcer with >50% stenosis	Yes	No	NA	NA

NA = not available, TIA = transient ischemic attack

*Joint Council of the Society for Vascular Surgery and the International Society for Cardiovascular Surgery (North American Chapter).
†Patients on aspirin therapy.

lished, the readers are referred to the specific publications that were compared.[53,54]

Surgery Quality Control

Carotid endarterectomy is a prophylactic operation to prevent stroke. This is the case for both symptomatic and asymptomatic patients. The effectiveness of the operation will vary inversely with the morbidity and mortality resulting from the operation. Thus, the lower the morbidity and mortality, the better the benefit-to-risk ratio with the operation compared with the natural history of the disease.

There is considerable variation in surgical results reported in the literature. Morbidity and mortality have been reported to range from 1% to 18%.[9,17-23,42] Recently a committee of the Stroke Council of the American Heart Association has published recommendations with regard to the upper acceptable limits of stroke morbidity and mortality as a function of indications for the operation. These limits should not exceed a combined morbidity and mortality of 3% when operating on patients with asymptomatic lesions, 5% in patients who undergo the operation for TIAs, 7% when the operation is performed for patients with a previous stroke, and 10% when the operation is being done for recurrent carotid stenosis.[24]

The audit and enforcement of these limits among surgeons in both community and institutional practice should have a major beneficial effect in assuring the best possible result of the operation with minimal morbidity and mortality. The vascular surgery community has made specific recommendations with regard to training, experience, hospital privileges, and periodic audit of those surgeons wishing to do vascular operations including carotid endarterectomy.[55-57]

Current Indications for Carotid Endarterectomy

From the previous discussion, it should be apparent that judging the indications for carotid endarterectomy remains fluid because several efforts at evaluation are still in progress. Nonetheless, and based on available data, it is possible to make some firm recommendations at this time. These recommendations will be based on the several units of analysis currently available and are summarized in Table 1. The indications listed in the table are based on the assumption that surgeons who do the operation can do so within the limits of morbidity and mortality set by the Stroke Council of the American Heart Association.[24]

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Articles

Misunderstanding in the Classification of Diabetes Mellitus

What's in a Name?

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To assess whether physicians, residents, medical students, hospital diagnosis coders, and patients properly use the designations insulin-dependent diabetes mellitus (IDDM) and non—insulin-dependent diabetes mellitus (NIDDM) that were established by criteria of the National Diabetes Data Group, we reviewed clinic and hospital records and administered questionnaires. Although essentially all cases of true IDDM were identified as such and most cases of NIDDM not requiring insulin therapy were correctly identified by all groups, patients with NIDDM on insulin therapy were misidentified as having IDDM by 38% of residents in internal medicine clinics and 68% of primary care and surgical subspecialty residents. On a survey, of 22 patients with NIDDM on insulin therapy, 17 (77%) considered themselves to have IDDM. Thus, patients who have NIDDM by the established criteria who are on insulin therapy are commonly mislabeled as having IDDM. We present an approach for dealing with this problem by adapting nomenclature focusing on insulin deficiency and resistance. It would probably also be helpful to separately identify the subset of patients with "insulin-deficient diabetes" who are ketosis-prone. It is important to use immunologic profiling (islet cell antibody testing) and insulin sensitivity or deficiency testing (C-peptide levels).

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"But 'glory' doesn't mean 'a nice knock-down argument,'" Alice objected.

"When I use a word," Humpty Dumpty said, in a rather scornful tone, "it means just what I choose it to mean—neither more nor less."

"The question is," said Alice, "whether you can make words mean so many different things."

"The question is," said Humpty Dumpty, "which is to be master—that's all."

LEWIS CARROLL
Through the Looking Glass, 1872

Although it has long been obvious that there are at least two different etiologic forms of diabetes mellitus, nomenclature for these different forms has changed several times. For many years, they were known as juvenile-onset diabetes mellitus and adult-onset diabetes mellitus. These terms were insufficiently precise, as a patient could have a condition physiologically equivalent to juvenile-onset diabetes with its onset at age 25 or 35 (certainly no longer juvenile) or the physiology of adult-onset diabetes with its onset in the teens. Thus, the terms "type I" and "type II" diabetes mellitus were developed, with a more precise pathophysiologic description. These terms were thought inadequately descriptive, so the terms insulin-dependent diabetes mellitus (IDDM) and non–insulin-dependent diabetes mellitus (NIDDM) were developed by the National Diabetes Data Group.[1] These last terms are now generally accepted and are widely used. Unfortunately, they are frequently misused and misunderstood. This alone would be of no consequence, but the inaccurate use has led to predictable problems in patient care, with ketosis-prone patients on adult services repeatedly receiving insulin far too infrequently and sliding into ketosis during their hospital stay. Insulin-dependent diabetes, originally intended to refer to ketosis-prone patients, has become expanded in common usage to apply to all patients on insulin therapy. We recognized the difficulty that medical students, residents, patients, and medical records coders had in correctly labeling patients with diabetes using the terms IDDM and NIDDM according to standards developed by the National Diabetes Data Group; therefore, we undertook this study to assess labeling of patients with diabetes by physicians, coders, patients, and laypersons.

Methods

To study this problem, we assessed six areas:

- The use of the terms for diabetes mellitus by residents in internal medicine clinic records;
- The use of the terms for diabetes mellitus by resi-

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ABBREVIATIONS USED IN TEXT

IDDM = insulin-dependent diabetes mellitus
NIDDM = non–insulin-dependent diabetes mellitus

dents in university hospital (university medical center) records;

- Coding of the hospital discharge diagnoses of patients by medical records coders in a university medical center;
- The identification of the type of diabetes by internal medicine faculty, residents, and students;
- Understanding of the terms for diabetes by patients with the disorder in internal medicine clinics; and
- Understanding of terms used for diabetes by adults attending a public education session to assess the level or ease of understanding of the terms by the general public, some of whom may have diabetes or are family members of those with diabetes.

The first three were assessed by medical records review, the last three by questionnaires. This study was approved by the Texas Tech University Health Sciences Center (Lubbock) Institutional Review Board.

Definitions

The criteria of the National Diabetes Data Group for IDDM and NIDDM were used as the gold standard for diagnoses of the type of diabetes mellitus in this study.[1] To summarize, IDDM was narrowly defined as ketoacidosis-prone diabetes (from autoimmune islet cell destruction) characteristically but not exclusively presenting in youths and normal-weight or thin persons. Definite NIDDM was defined as diabetes mellitus occurring with a strong component of resistance, often in an obese person, usually beginning after age 40, frequently with some history of the successful use of diet or oral agents, and with no ketoacidosis (except starvation ketosis).[1-3] Although the age of onset is not a criterion, this proved so predictive in one study[3] that it was used to help classify patients. A diagnosis of "indeterminate" was assigned to those cases where information was insufficient to decide whether the patient had IDDM or NIDDM and for those persons who did not meet the clear-cut criteria for either group. The terms "diabetes," "juvenile-onset diabetes," "adult-onset diabetes," "type I," and "type II" were simply accepted as used in the medical records, by physicians, or by patients.

Medical Records

Clinic charts. In all, 358 records were reviewed over a nine-month period in a university medical clinic. Those records with any form of diabetes on the problem list were pulled for direct review. Information recorded and analyzed for these charts included age, ethnic origin, and sex of the patient, age and presence or absence of obesity at the time of the diagnosis of diabetes, the use of insulin, the use of diet alone or oral agents to control the diabetes, a history of ketoacidosis, and the use of each of the terms for diabetes by each of the physicians seeing the patient. The data available in the medical record were used to assess whether a patient had IDDM or NIDDM or whether it was indeterminate by the data available.

Hospital charts. Medical records from all patients having any form of diabetes mellitus as a discharge diagnosis from the Texas Tech University Health Sciences Center were identified, and a 100-chart sample was selected for review. Of these, 13 were duplicate entries, 3 were misidentified in some way, and 6 were not available for evaluations, leaving a 78-chart sample from this population, which was reviewed as described earlier. Also noted was whether the patient was on primary care services (internal medicine, pediatrics, or family medicine) or surgery and surgical subspecialties (anesthesiology, ophthalmology, orthopedics, and gynecology). The coded diagnosis (IDDM or NIDDM) was recorded at the time of the hospital records review.

Professional Understanding of Terms

Attending physicians, residents, and students attending (unrelated) medical grand rounds were asked to assign the type of diabetes—IDDM, NIDDM, juvenile- or adult-onset, type I, type II, or indeterminate (multiple answers allowed)—to the following series of case vignettes:

1. A 5-year-old with ketoacidosis and diabetes,
2. A 30-year-old with a new onset of ketoacidosis and diabetes,
3. A 60-year-old obese woman with diabetes for 20 years who has been on insulin therapy for 15 years, and
4. A 40-year-old with diabetes who has been taking oral agents for 20 years.

The case vignettes were designed to represent classic and easily identified IDDM (case 1) and NIDDM (case 4) and easily confused IDDM (case 2) and NIDDM (case 3).

Patient Survey

A total of 45 patients attending internal medicine clinics identified in their records as having diabetes were given a questionnaire to record their age, sex, education, diabetic education, age at diagnosis of their disease, the presence of obesity at the time of the diagnosis, their use of insulin, their use of oral agents, their use of diet alone, history of ketosis or ketoacidosis, and which terms they used to describe their diabetes (multiple answers allowed).

General Public Survey

About 148 persons attending a medical information seminar were given questionnaires with lay versions (omitting the word "ketoacidosis" in case 1 of vignettes) and were asked to choose appropriate labels, with multiple answers allowed to assess whether these terms are currently or easily understood by the general public. Case 2 was not used because it was thought to require a degree of medical sophistication to understand.

Data Analysis

The data from each of these sources were analyzed to assess whether there was adequate information—such

TABLE 1.—*Resident Physicians' Diagnoses of Diabetes Mellitus in 76 Patients Seen in Internal Medicine Clinic*

NDDG Diagnosis*	Resident Physicians' Diagnosis, No. (%)			
	IDDM	NIDDM	Diabetes Mellitus	Both IDDM and NIDDM
Insulin-dependent diabetes mellitus (IDDM), n = 9	9 (100)	0 (0)	0 (0)	0 (0)
Non–insulin-dependent diabetes mellitus (NIDDM), no insulin therapy, n = 31	0 (0)	26 (87)	5 (13)	0 (0)
NIDDM plus insulin therapy, n = 32	12 (38)	11 (34)	7 (22)	2 (6)
Indeterminate, n = 4	4 (100)	0 (0)	0 (0)	0 (0)

*The diagnosis was established by criteria of the National Diabetes Data Group (NDDG).[1] "Indeterminate" refers to those cases for which insufficient information was available to assign a clear-cut diagnosis.

as the use of insulin, weight and age at diagnosis, or a history of ketoacidosis—to assign a label of "IDDM," "NIDDM," or "indeterminate" by the National Diabetes Data Group criteria.[1-3] These labels were then compared with those used by the physicians, patients, or coders. The information was reviewed to determine if there were any systematic biases in the use of these terms.

Results

Records Review

Clinic charts. A total of 358 medical records from October 1989 through June 1990 were reviewed, and 76 cases of diabetes mellitus were identified. Of these, 9 were clear-cut insulin-dependent diabetes; all were correctly identified by this term. "Type I" was also used correctly on one chart (Table 1). Internal medicine residents incorrectly labeled about 12 patients (38%) with NIDDM on insulin therapy as having IDDM.

Hospital charts. In all, 1,084 medical records had discharge diagnoses of "diabetes" for 1990. From these, a sample of 78 were reviewed as described earlier (Table 2). Five records lacked sufficient information to allow a classification of IDDM or NIDDM; all were on insulin therapy, and all were called IDDM by physicians and coded as IDDM. There was no difference in the use of terms by physicians in primary care versus those in surgery and surgical subspecialties. Thus, whereas true IDDM was always correctly identified by physicians and coders, in only 11 of 50 patient records (22%) coded as IDDM were the cases true IDDM. Physicians were more accurate than coders and did not misidentify any patients who were not on insulin therapy as having IDDM, but they did mislabel 68% (26 of 38) of patients with NIDDM on insulin therapy.

Physician Survey

Of a total of 56 physicians (34 attendings and residents) and medical students (14 third- and fourth-year students) who attended medical grand rounds, 48 returned questionnaires. Of the physicians, only 1 labeled the child with ketosis (case 1) as having NIDDM (Table 3).

On case 2 (a 30-year-old with ketoacidosis and diabetes), of the 28 physicians choosing between IDDM and NIDDM, all but 1 chose correctly; of 21 using the terms type I or type II, again all but 1 chose correctly.

For case 3 (60-year-old woman with diabetes for 20 years who had taken insulin for 15 years), of the 21 physicians using the terms IDDM or NIDDM, 17 used the correct term; they all correctly identified it as adult-onset diabetes; and of 24 using the terms type I or type II, 23 correctly identified type II. Of the medical students, 8 identified NIDDM, all used the term adult-onset, and 10 of 12 choosing between types I and II correctly identified type II.

For case 4 (40-year-old man with diabetes on oral diabetic therapy for 20 years), none of the physicians used an incorrect term. Of the medical students, all choosing between IDDM and NIDDM chose correctly, and 1 of 8

TABLE 2.—*Discharge Diagnoses of Diabetes Mellitus on a Sample (n = 78) of Medical Records, by Different Terms and Physician Specialty*

NDDG Diagnosis*	Diagnosis on Chart, No. (%)				Coded Diagnosis, No. (%)	
	IDDM	NIDDM	Diabetes Mellitus	Other	IDDM	NIDDM
Insulin-dependent diabetes mellitus (IDDM), n = 11	11 (100)	0 (0)	0 (0)	0 (0)	11 (100)	0 (0)
Non–insulin-dependent diabetes mellitus (NIDDM), no insulin therapy, n = 24	0 (0)	15 (68)	8 (33)	1 (4)	2 (8)	22 (92)
NIDDM plus insulin therapy, n = 38	26 (68)	8 (21)	2 (5)	2 (5)	37 (97)	1 (3)
Primary care residents	15	5	0	2		
Surgical residents	11	3	2	0		
Indeterminate, n = 5	5 (100)	0 (0)	0 (0)	0 (0)	5 (100)	0 (0)

*The diagnosis was established by criteria of the National Diabetes Data Group (NDDG).[1] "Indeterminate" refers to those cases for which insufficient information was available to assign a clear-cut diagnosis.

TABLE 3.—*Type of Diabetes Mellitus Diagnosed by Physicians (n = 34) and Students (n = 14) for Fictional Case Vignettes**

	Terms Used to Diagnose Diabetes, No.						
Case†	Insulin-Dependent	Non-Insulin-Dependent	Juvenile Onset	Adult Onset	Type I	Type II	Not Specified
Physicians							
1	18	1	21	0	19	0	5
2	27	1	3	4	20	1	1
3	4	17	0	22	1	23	0
4	0	23	0	12	0	19	7
Students							
1	6	0	8	0	9	0	2
2	7	4	2	5	4	5	0
3	2	8	0	10	2	10	0
4	0	9	1	7	1	8	0

*Multiple answers were allowed, so columns add up to more than total number.
†Cases 1 and 2, as described in text, had insulin-dependent diabetes mellitus; cases 3 and 4 had non-insulin-dependent diabetes mellitus.

incorrectly identified juvenile-onset diabetes or the term type II diabetes.

Overall, incorrect terms were chosen by 4% of the respondents for case 1, 23% for case 2, 19% for case 3, and 4% for case 4. For all cases, the terms IDDM or NIDDM were chosen and used correctly in only 60% of the answers. Physicians and medical students in internal medicine are somewhat confused by the plethora of terms available for the types of diabetes, especially for insulin-treated adult patients.

Patient Survey

Of 45 patients attending the residents' clinic in internal medicine identified as having diabetes and given the questionnaire, 33 completed it. The three patients with IDDM checked their condition as juvenile-onset diabetes, two as IDDM, and one as type I (all used some correct term, multiple answers allowed). Of the eight patients with NIDDM on no insulin therapy, six checked adult-onset diabetes (the other 2 were unfamiliar with the terms juvenile- or adult-onset diabetes), two checked type II (the other 6 were unfamiliar with this term), four checked NIDDM, two checked IDDM (even though they were not on insulin therapy), and two were not familiar with these terms.

Of the 22 patients with NIDDM on insulin therapy, 14 used the term adult-onset diabetes, with the remainder being unfamiliar with these terms; 7 checked type II, 1 type I, and the other 14 were unfamiliar with these terms; and 3 checked NIDDM, 17 IDDM, and 2 were unfamiliar with these terms. Thus, 100% of patients choosing between juvenile- or adult-onset diabetes chose the correct term; 88% of those choosing between types I or II were correct, but only 15% of those choosing between IDDM or NIDDM were correct. Overall, of the 21 patients saying they had IDDM, only 3 (14%) definitely had it.

Public Survey

About 148 questionnaires were distributed, of which 44 were returned completed. For case 1, 40 identified a correct term (Table 4). Of 10 respondents who had diabetes, 9 chose an appropriate term. For case 3, only 6 chose a combination of correct terms. All used the term adult-onset diabetes correctly, but only 5 of 33 choosing between IDDM and NIDDM chose the correct term. Likewise, of 19 choosing between types I and II, only 14 were correct. Of the ten with diabetes, only one chose correct terms. Overall, of those choosing IDDM or NIDDM, 63% used these terms correctly (albeit only 15% used these terms correctly for an obese adult with diabetes not prone to ketosis and on insulin therapy).

Discussion

Much effort has been expended over the years to devise succinct and accurate labels for the different types of diabetes. Clinically, two major subgroups, long known as juvenile-onset and adult-onset diabetes, have been noted, but these terms were sometimes misleading. Alternative terms, type I and type II, then insulin-dependent and non-insulin-dependent diabetes, are now used.[1] Whereas

TABLE 4.—*Survey of Laypersons' Understanding of Terms for Diabetes Mellitus (n = 44)**

	Terms Used for Diabetes Mellitus						
Case†	Insulin-Dependent	Non-Insulin-Dependent	Juvenile-Onset	Adult-Onset	Type I	Type II	Not Specified
1	22	3	37	0	21	0	0
3	28	5	0	25	5	14	4
4	2	28	4	23	5	10	0

*Multiple answers were allowed, so columns add up to more than total number of respondents.
†Case 1, as described in text, had insulin-dependent diabetes mellitus; cases 3 and 4 had non-insulin-dependent diabetes, with case 3 on insulin therapy. Case 2 used terms considered too technical for laypersons and thus was not included.

these last terms are now widely used, they are probably even less acceptable than the previous "juvenile-type" and "adult-type" diabetes were, as patients, physicians, and medical records coders frequently use these terms incorrectly. Although true IDDM was almost always correctly identified as such in this study by patients, physicians, and coders—as was NIDDM requiring diet or oral agent therapy—patients with NIDDM on insulin therapy were misidentified as often as not. It is exceedingly difficult to teach physicians to use these terms correctly: The medical students had had at least two to three hours of lecture in the second year on the clinical aspects and classification of diabetes and yet were correct only 64% of the time for any term and only 53% when choosing between IDDM and NIDDM. Patients and laypersons were even less accurate in the use of the terms. Not surprisingly, they did much better with the terms juvenile- and adult-onset diabetes. It is easy to understand why an obese patient on insulin treatment from age 60 to 70 (although taking oral agents for 10 years before that) would think that they had insulin-dependent diabetes. Explaining this concept to medical students or allied health professionals takes one to two hours and much basic science background. Moreover, there is some professional controversy in this area.[2] Some physicians consider that recurrent high glucose levels or hyperglycemic hyperosmolarity without ketosis is indicative of insulin dependence (not part of the National Diabetes Data Group criteria). The American Diabetes Association further confuses the issue by the following statement on type II diabetes: "Insulin may be required *at times* for control of *transient,* stress-induced hyperglycemia or hyperglycemia that persists in spite of other therapy"[4(p5)] (emphasis added). This statement does not convey any impression that 30% to 70% of patients with NIDDM may be on long-term insulin therapy. The criteria of the National Diabetes Data Group for NIDDM are such that classifying patients on insulin therapy is often difficult.[2] With such disagreement among physicians, it is no wonder that patients and students so often misuse the terms.

Thus, despite more than a decade of use, the terms IDDM and NIDDM are misunderstood and misused, not only by patients and laypersons (possible patients and family members), but also by physicians. This problem seems to devolve from two sources: the terms are not inherently obvious, and many specialists disagree as to what they mean. As to the latter reason, whereas there is general agreement that diabetic patients who are prone to ketoacidosis have IDDM, physicians disagree about whether a mildly obese patient who is noncompliant with diet and who has glucose levels of 16.7 to 22.2 mmol per liter (300 to 400 mg per dl) has NIDDM or IDDM. Moreover, these terms are inadequate for another reason: they do not provide unambiguous information about cause or treatment. If anything, they cloud this issue and may produce more harm than good. For instance, an unfortunately common scenario at Texas Tech University is that of a patient with ketoacidosis-prone diabetes admitted to hospital and kept off oral intake because certain tests need to be done, who "slips" into ketoacidosis while glucose levels are "under control" because the house staff, who are accustomed to seeing non–ketosis-prone, insulin-treated patients, monitor the glucose levels only and fail to use insulin at sufficient intervals to prevent ketoacidosis. Meanwhile, insulin is overused in obese patients with glucose levels of around 16.7 mmol per liter without an adequate emphasis on dietary and exercise management.

Other terms that have been proposed include "diabetes mellitus, predominant insulin deficiency" and "diabetes mellitus, predominant insulin resistance."[5] These terms more effectively convey the underlying pathophysiology and point to the management. Their awkwardness could be ameliorated by using the core terms "deficient" and "resistant." This suggestion, however, is open to the criticism of reinforcing negative self-labeling in patients with diabetes. Another possible criticism is the difficulty of exact differentiation and diagnosis. This is not substantially different from the difficulty with currently used categories, as there are clear-cut cases of IDDM and NIDDM and more ambiguous cases. Also, they do not address etiologic categories or therapeutic differences.

Many studies have indicated that early intervention with immunosuppressants or intensive insulin therapy ameliorates the course of immunologically mediated, insulin-deficient diabetes.[6-8] In addition, other studies show that about 15% of persons with adult-onset diabetes have immune markers (islet cell antibodies) without ketoacidosis-prone diabetes.[9-14] These studies suggest that the early identification of immunologically mediated diabetes is important and that patients without diabetic ketoacidosis are at risk. Thus, a classification system that focuses on cause could be therapeutically meaningful. At any rate, testing for islet cell antibodies in patients with new-onset diabetes that is not the classic NIDDM of obesity would seem to be warranted.

The degree of insulin deficiency as manifested by C-peptide levels also appears to play a role in the appropriate management of diabetes.[15-24] Insulin resistance appears to play a major role in obese patients with diabetes.[18-25] Determining insulin resistance in patients can be complicated, but clinical measurements such as weight and possibly insulin or C-peptide levels are predictive.[15-24] Aggressive dietary management, which can often control NIDDM,[25] is difficult for many patients to afford—as in very-low-calorie liquid diets—or to comply with. It is unclear whether the control of glucose levels by insulin in the absence of dietary compliance is of benefit. Alternative oral agents (metformin, when available) and the use of appetite suppressants may be of more benefit for long-term management.

Another problem of the currently used terms is the mixed population of NIDDM in research studies. Thin or nonobese patients with NIDDM often have a mixture of partial deficiency (often on an autoimmune basis),[9-21] "metabolic obesity,"[26] and genetic resistance. It is not surprising that studies of such patients reveal heterogeneity or findings different from those of obese patients with NIDDM, who are probably (mostly) insulin-resistant. It is

therefore important for studies of patients currently labeled as having NIDDM to provide further data on their populations including islet cell antibody studies and probably some assessment of resistance—admittedly a fluctuating variable. A classification focusing on the direct determination of these contributing causes would be important in our understanding of diabetes but may be too cumbersome for routine clinical management.

Whereas many persons with "resistant" diabetes show increased ketosis,[27,28] only those with insulin-deficient diabetes have recurrent problems with diabetic ketoacidosis and must receive insulin at regular intervals even with normal glucose levels to prevent this. Mismanagement is common in this area, and management could perhaps be improved by a classification based on this problem—"ketoacidosis-prone" diabetes as a subgroup of insulin-deficient diabetes.

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Articles

Rehabilitation Services for the Pacific

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The Pacific Basin Rehabilitation Research and Training Center was created to help meet the challenges of rehabilitating people in rural remote communities in the United States-associated Pacific. We describe the center, the special region it serves, some of its many programs, and some of the ways it is helping communities in this region provide services that are appropriate and sensitive to the culture, the environment, and the disability.

(Fitzgerald MH, Barker JC: Rehabilitation services for the Pacific. West J Med 1993; 159:50-55)

Culturally distinct groups of people, especially those in remote communities, have unique needs and present special challenges for providing medical and rehabilitation services. Island nations in the Pacific Basin are remote, rural, diverse, and therefore challenging.

Case Examples

Case 1

JP is from a small island in the complex of islands known as Chuuk (formerly Truk). In 1982, when he was 14, he fell off a waterfall and had a cervical spine injury that left him quadriplegic. He was air evacuated to Honolulu, Hawaii, and transferred to the Rehabilitation Hospital of the Pacific. The cost of his care was over $70,000, which represents a substantial portion of Pacific island community health budgets for an entire year. For example, in 1988 the health budget for the jurisdiction in which JP lived was $246,000.[1] Thus, the cost of his care was 28% of the entire health care budget.

The monetary cost represents only one of the many extraordinary costs involved, for social, familial, and personal costs were equally high. He was sent to a foreign environment—not just the hospital but Hawaii itself—where he spent more than a year thousands of miles from his support network of family and friends and away from familiar foods, language, and culture.

When JP finally returned home, he was an anomaly in his community, and it did not know how to respond. People tried to treat him as someone sick and dependent, but he felt neither sick nor dependent. In fact, during his stay at the rehabilitation hospital, he had been trained to be independent. When his family tried to comply with his desire for independence, the community judged his family as not fulfilling their responsibilities. All of this was further exacerbated when JP insisted on returning—alone—to his high school on another island. His behavior, and that of his family for allowing him to go despite their misgivings, was viewed by island neighbors as not being proper disability-related behavior. The patient's independent attitude itself was enough to make his neighbors uncomfortable because independence is often not understood by Pacific Islanders, who rely on and value interdependence.

Case 2

JR lives on another rural Pacific island, similar to that of the first case. Both are nearly the same age and have similar levels of injury and impairment. When JR dove off a bridge and injured his cervical spine in 1989, however, he did not have to leave his community for either acute or rehabilitation care. Because of important changes in the nation's ability to care for people with such injuries, including the presence of a trained rehabilitation technician, this patient's rehabilitation took place in a familiar environment.

The family, rather than nurses, provided much of his care. Family also provided his food, assisted with personal care, and stayed with him throughout his hospital course. From the time of his injury, JR's family was an important component of the rehabilitation effort; they were part of "the team." Supported by the wider community, they worked with the rehabilitation technician in meeting JR's health, social, and rehabilitation needs.

When he left the hospital, JR was unable to resume the usual activities of young men in his community—climbing coconut trees, farming, and fishing. A wheelchair shipped from Hawaii allowed him to move about the one western-style building with a cement floor in his household compound, but the rough terrain around his home restricted his mobility, and he was dependent on his family to carry him outside. Nevertheless, he was soon reintegrated into the household and took on the socially acceptable role of supervising the younger children, freeing others to do tasks he might have done.

Although an exact figure is not available, the cost of this patient's care was considerably less than that of the first case. One of the largest expenditures was for the wheelchair and the cost of shipping it.

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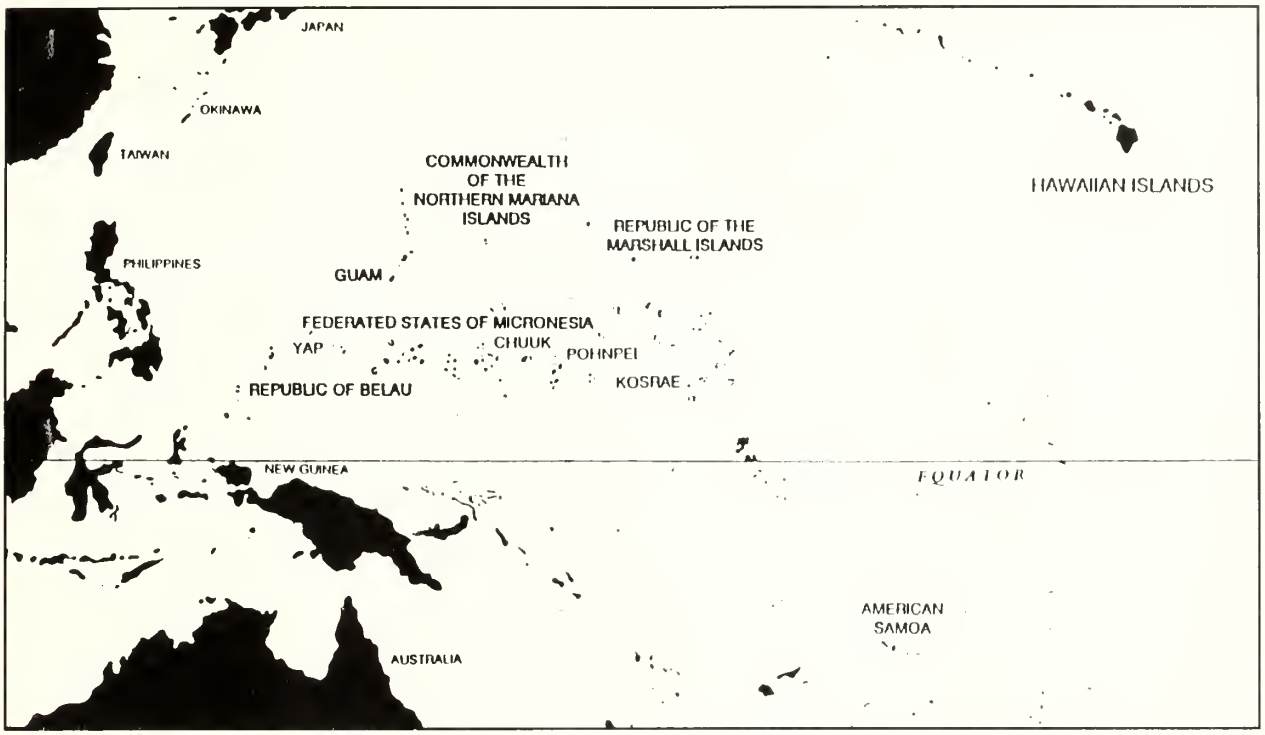

Figure 1.—The map shows the service area of the Pacific Basin Rehabilitation Research and Training Center.

How and why was such a dramatic change in the approach to rehabilitation possible? Providing rehabilitation services in the Pacific Basin encompasses three challenges: the communities are in rural or remote areas; the populations are diverse with differing needs; and services need to be culturally, environmentally, and disability-appropriate and sensitive. The Pacific Basin Rehabilitation Research and Training Center (PBRRTC) was designed specifically to help address these challenges.*

Pacific Service Area

The United States-associated Pacific Islands comprise Hawaii, American Samoa, Guam, and what was formerly known as the Trust Territory of the Pacific Islands. The area is as large as the continental United States, roughly 7.8 million km² (Figure 1). But unlike the US mainland, the region is composed almost entirely of water, which creates transportation and communication problems.

Sociodemographic Diversity

Diversity best describes the region—diversity in geography, population, demography, environment, and health needs and medical services. The population of about 1.5 million represents a varied group of Pacific, Asian, and European cultures spread over more than 100 inhabited islands ranging from tiny atolls barely above sea level to large, high volcanic islands.[2] Even adaptation to the tropical island and ocean environments—to heat, humidity, sandy and coral soils, and salt air—has not been uniform. Rather, many different housing, fishing, and agricultural forms have arisen.[2,3]

Divided into seven politically distinct units (Table 1),[4-7] all jurisdictions are a collectivity of islands, sometimes with far-flung outliers. All have culturally diverse populations, the most heterogeneous being in Hawaii, Guam, and the Northern Marianas. The other four political units are less culturally varied, being dominated by people of either Micronesian (Belau [formerly Palau], Federated States of Micronesia, Marshall Islands) or Polynesian (American Samoa) origin. At various times and locations, Spain, Germany, and Japan administered these islands until the United States took over, each leaving behind cultural vestiges.

There is great diversity in language; in Micronesia, for example, there are at least nine different languages. Most people are bilingual, and many are multilingual. English is the official language of government throughout the region.

The history, ecology, and social structure of each island group differ somewhat; nevertheless, similarities can be found in cultural values, beliefs, social organization, life course, and behavior.[2,3,8] Central themes of common importance are as follows: a great emphasis on family and community rather than on the individual; a strong, traditionally based system of social ranking, usually with men being more politically important than women; individual achievement and honor often tied to family rank, which in turn is tied to owning land.

The population size of most of these Pacific islands is

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TABLE 1.—*Sociodemographic Characteristics of United States-Associated Pacific Basin Countries, 1988 to 1990**

Jurisdiction	*Political Status*	*Ethnic Heritage*	*Land Mass, km²*	*Population*	*Population Density, /km²*	*Urban Population,† %*	*Annual Population Growth Rate, %*	*Adult Literacy Rate, %*	*Life Expectancy at Birth, yr*	*Crude Birth Rate, /1,000*	*Crude Death Rate, /1,000*	*Infant Mortality Rate, /1,000 live births*	*Rural Population With Safe Water, %*
Hawaii	US State	Polynesian, mixed	16,690	1,108,229	66.4	NA	NA	95‡	75‡	17.3‡	5.5‡	7.2‡	100
American Samoa	Territory	Polynesian	197	46,773	237.4	34	1.9§	NA	70§	29.7	4.3	8	NA
Guam	Territory	Micronesian, mixed	541	107,819	199.3	70	2.2	96	72	26.3	3.7	7.5	100
Northern Mariana Islands	Commonwealth	Micronesian, mixed	476	49,952	92.3	79	3	95	66	37.9	5.9	19	85
Marshall Islands	Republic	Micronesian	176	46,188	262.4	47	4	NA	61	49.2	3.6	63	NA
Belau (Palau)	Republic	Micronesian	494	15,122	30.6	62	1.4	75-85	66§	21.8	7.5	26	95
Federated States of Micronesia	Federation of States	Micronesian	686	103,723	151.2	23	1.8	50	58§	23.8	NA	18	60
Chuuk (Truk)	State FSM		127	48,000	378.0	--	--	--	--	--	--	--	--
Kosrae (Kusaie)	State FSM		100	7,000	70.0	--	--	--	--	--	--	--	--
Pohnpei (Ponape)	State FSM		345	28,000	81.2	--	--	--	--	--	--	--	--
Yap	State FSM		119	11,000	92.4	--	--	--	--	--	--	--	--

NA = (data) not available

*From Rotem and Dewdney, 1991.[4] †From Connell, 1987.[5] ‡From the Bureau of the Census, 1991.[6] §From Taylor et al, 1991.[7]

modest to small. In a few places with little land (Chuuk state, American Samoa), however, population densities are unexpectedly high (see Table 1). Some nations, such as the Federated States of Micronesia, have no huge, centralized urban center with commercial amenities or government services, whereas others, such as Guam, support modern cities. Some polities have both cities and remote, rural areas, such as Hawaii, where there are modern cities like Honolulu and areas like Molokai that are remote and underdeveloped. Some jurisdictions are strongly enmeshed in a cash economy (Hawaii), and others (the Marshall Islands) are based on subsistence agriculture and fishing.

Sociodemographic factors also indicate wide variations among Pacific communities, for example, in rates of natural increase, birth, death, and infant mortality; literacy; supply of safe water to rural villages; and life expectancy. For some communities, such as the Marshall Islands, the sociodemographic profile is similar to that of most underdeveloped nations, and others, such as Guam, compare favorably with mainland metropolitan areas (see Table 1).

Health Profiles

Country health profiles, medical and rehabilitation services, and resources are also diverse, as Table 2 shows.[4,6,9] These are relatively poor jurisdictions with small per capita health expenditures. Health indicators such as the leading causes of death and infant mortality rates vary considerably. Hawaii has a health and mortality profile similar to that of the US mainland, whereas the profiles for some other island groups (Federated States of Micronesia) are more like those of typical third world nations. Besides similar values, beliefs, and behaviors, these Pacific communities share expanding populations and increasing ill health.

Rehabilitation Services

The epidemiologic transitions[7,9,10] that have accompanied modernization in these communities have dramatically increased the need for rehabilitative services and disability prevention programs.[11,12] The prevalence of strokes, diabetes mellitus, injuries, chronic pain syndromes, and other potentially debilitating conditions is rapidly increasing—and dramatically so among younger age groups—40- to 50-year-olds are having strokes and 15- to 30-year-old men have high rates of suicide, homicide attempts, and traumatic injuries, especially from motor vehicles.[7-9]

Some communities, like Hawaii, have well-developed rehabilitation service systems comparable to most large mainland US cities. In other communities, however, rehabilitation service systems are modest in size and design. Kosrae (also called Kusaie), the most modest, for example, has one hospital run by the state, one rehabilitation technician, a Crippled Children's Service coordinator, and a geriatric home health care coordinator.[13]

Yet another commonality has a substantial effect on the provision of services. All these jurisdictions are asso-

ciated with the United States. This means that the service delivery models were generally introduced and are often maintained by professionals trained in the United States and that many of the programs are funded by the US government. An acceptance of federal funding is accompanied by the requirement to comply with federal mandates. Such mandates include rules, regulations, and guidelines generally developed by and for the American urban (generally white) middle class and thus are guided by their values and perceptions of needs and resources.

There is little reliable information on disability-related beliefs, practices, and attitudes of Pacific Islanders. People who have worked in the area generally agree that these differ considerably from those of the mainland United States and within the region itself. Cultural beliefs about illness, social relationships, and appropriate behavior, as well as island life-styles, clearly influence ideas and practices around disability. Consequently, it sometimes seems difficult or nearly impossible to provide culturally relevant, sensitive, and appropriate services while meeting US mandates.

This disjuncture between mainland and Pacific Islander ways of viewing and responding to disability and the failure of mainland models to adequately serve Pacific rehabilitation needs were recognized by officials in the island communities. Thus, they hired their own personnel and asked PBRRTC to devise guidelines and provide training for these rehabilitation technicians that was appropriate to Pacific social, cultural, and economic norms.

Pacific Basin Rehabilitation and Research Training Center

The PBRRTC is a community-oriented program affiliated with the John A. Burns School of Medicine at the University of Hawaii and housed at the Rehabilitation Hospital of the Pacific in Honolulu. It is one of 39 such centers funded by the US Department of Education's National Institute on Disability and Rehabilitation Research. Funded in 1984, PBRRTC is one of a small group of centers with a regional or minority group focus and the only one with a focus on the Pacific region. Most other centers deal with either a categorical disability (spinal cord injuries, stroke, and brain injury) or a disability-related issue (families and disability, or rural rehabilitation).

The goals of the center are "to improve services to individuals with handicaps through relevant research and training in the Pacific Basin and to assist in the coordination of rehabilitation services provided by a broad range of agencies and entities."[14] The center does not itself provide rehabilitation services. Its goals are accomplished through various research and training programs in cooperation with other agencies and the communities involved. The programs focus on training service professionals and on providing technical and research assistance to help communities identify rehabilitation needs and resources and develop culturally appropriate rehabilitation service delivery models.

TABLE 2.—*Health Profile and Health Economics of United States-Associated Pacific Basin Countries, 1989 to 1990**

	Hospitals		Medical Officers		Health Budget			Proportional Mortality by Cause†				
Jurisdiction	*No.*	*No. of Beds (/1,000)*	*Total*	*Ratio/ Capita of Population*	*Total in millions, $US*	*Per Capita Expenses, $US*	*Portion of Total Budget, %*	*Infections, %*	*Cancer, %*	*Cardiovascular, %*	*Respiratory, %*	*Perinatal, %*	*External, %*
Hawaii	26	4,000 (2.5)	2,493	1:445	NA	NA	NA	1‡	25‡	38‡	6‡	NA	7‡
American Samoa	1	117 (2.5)	25	1:1,871	NA	NA	NA	1	16	30	13	4	21
Guam	1	154 (1.2)	163	1:814	78.1	607	NA	1	23	37	4	4	12
Northern Mariana Islands	1	74 (1.95)	19	1:2,000	24.6	648	21	4	10	35	11	12	16
Marshall Islands	2	110 (2.38)	NA	NA	NA	NA	NA	14	12	17	9	20	8
Belau	1	60 (4.3)	11	1:1,273	2.3	153	10	5	18	27	13	10	19
Federated States of Micronesia	4	308 (3.1)	38	1:2,526	12.2	117	13.4	22	9	12	14	5	16
Chuuk§	1	125 (2.6)											
Kosrae§	1	35 (5.0)											
Pohnpei§	1	98 (3.5)											
Yap§	1	50 (4.5)											

NA = [data] not available

*From Rotem and Dewdney, 1991.[4]
†From Taylor et al, 1989.[3]
‡From the Bureau of the Census, 1991.[6]
§From the Pacific Island Health Officers' Association Maternal and Child Health Strategy Data Base, Region IX US Public Health Service and World Health Organization Country Health Information Profile (written communication, June 1992).

For example, PBRRTC provides technical assistance to the State of Hawaii's Department of Vocational Rehabilitation in needs assessment research and is working with Hawaii's Department of Health investigating injuries. Research projects with Hawaii's Rehabilitation Hospital include such things as aging with a disability (such as from late effects of polio) and hip fractures among older adults. The center also provides planning and financial support for educational programs, gives seminars on Pacific Basin rehabilitation needs and activities, and acts as a general resource center for people providing services to Pacific Islanders.

While the Hawaii projects are important, PBRRTC's efforts are most distinctive in other parts of the region and more clearly driven by cultural issues. Outside Hawaii, for the most part, PBRRTC's efforts are divided between departments of health and the departments of vocational rehabilitation in those areas that still have federally funded vocational rehabilitation programs, such as Guam, Northern Marianas, Belau, and American Samoa.

One of PBRRTC's primary programs is the training of rehabilitation technicians.[15,16] Indigenous personnel are trained to provide technically competent and culturally appropriate rehabilitation services in their home communities. Before this program, many of the smaller communities had no trained rehabilitation service professionals. Thus people often either received no rehabilitation services or—like case 1—were transported off-island, usually to Hawaii, at great expense.

Rehabilitation Technician Training

There are now ten rehabilitation technicians serving their communities— 2 each in American Samoa, the Marshall Islands, and Yap state; 1 in Belau; and 1 in each of the other states of the Federated States of Micronesia. Altogether, they care for about 1,300 people a year ranging in age from 2 months to 93 years, and they provide roughly 12,000 treatment sessions.[16] Such numbers underestimate the benefits of this program, however, because much of their work is done informally, especially in raising community awareness and in teaching family members to care for a rehabilitation patient—as in case 2.

Although most of the work of these technicians constitutes physical therapy, they are more broadly trained because PBRRTC staff represent many health-related professions—occupational and physical therapy, nursing, and social work. Because many PBRRTC staff have experience working with Pacific Islanders and are aware of the special cultural and environmental factors associated with these populations, they have been able to translate their formal training into skills and concepts useful in an atoll or island setting.

Most rehabilitation technician training takes place within the community on a one-to-one basis. Once a year, however, the technicians are brought together as a group to undertake additional training. Some traditional classroom sessions occur, but observational and experiential learning is the hallmark of the training program as this is more consistent with the traditional learning style of Pacific Islanders. Training is directed toward individual trainees' needs and the special needs of their community and patients.

Although the rehabilitation technician training program is financed with US federal funds, the technicians are under the jurisdiction of their local governments and, therefore, do not have to conform to federal mandates—unlike vocational rehabilitation counselors and other rehabilitation service professionals funded directly by the US government. This independence allows the technicians (with the assistance of PBRRTC staff) the latitude to translate skills and knowledge into culturally meaningful and appropriate services.

Culturally Appropriate Services

In Guam and Saipan in the Northern Marianas, which are undergoing rapid development in response to the tourist industry, unemployment is low. But in more rural, remote communities (like the island of Molokai in Hawaii, or Belau or Kosrae), there are few cash-paying positions and many applicants. In these remote communities, productive activity more often centers on family enterprises, usually farming, fishing, and, occasionally, small retail stores. Narrowly defined, a homemaker closure means that at the end of the technician's involvement, the client's principal activity is keeping house or working as an unpaid family worker in a family enterprise such as a farm or a business. Thus, the number of cases with "homemaker" closures, viewed by some rehabilitative workers as a low status closure, may be high by urban, US standards, but is entirely appropriate by island standards.

Some Pacific island vocational rehabilitation expenditures are unusual by the standards of mainland Americans, such as the purchase of a machete or of a piglet and some feed. These items allow rural Pacific Islanders to make major contributions to their family's welfare, as a machete is essential for island farming and harvesting from the bush, and pigs are not only a source of food, they have great symbolic value. Being able to raise large pigs, especially for ceremonial purposes, is highly prized and can elevate a person's status within the community. Likewise, the purchase of a boat for a client living on an island not only provides an opportunity for him or her to engage in subsistence fishing, perhaps even catching enough excess to sell a few at market, it also provides transportation to other job opportunities and to services such as health care. Mainland Americans need to be aware that people other than the client will use this boat. It would be culturally unacceptable for a Pacific Islander to refuse to loan a boat, especially to family or close kin. When the client is in a position to share a precious resource, he or she can make a substantial and culturally appropriate contribution to family and community welfare that in turn reinforces that person's role and status as a capable, productive adult. This kind of community and familial orientation of values and activities may seem alien to people from a society that values independence, but becoming

aware of such values is critical to developing and providing culturally relevant and appropriate training and services to Pacific Islanders.

Conclusion

Rehabilitation service delivery models, standards of care, and regulations developed for one population are not always appropriate for other groups. There is a growing awareness of the need for cultural awareness and sensitivity, but there is still little information on how to incorporate these into the development and provision of health and rehabilitation services.

This brief description of the Pacific Basin Rehabilitation Research and Training Center and some of its programs shows how one organization is helping communities serve the needs of people with disabilities in a culturally meaningful way. While this organization's focus is the Pacific Basin, other rural communities and culturally distinct populations within mainland America, such as American Indians, have similar needs for culturally appropriate and sensitive rehabilitation services. Providing services in rural, remote communities is a special challenge that requires new, creative, and flexible approaches. Many of PBRRTC's programs can serve as models to be adapted for use elsewhere.

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Conferences and Reviews

Neuroplasticity
Key to Recovery After Central Nervous System Injury

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After an injury to the central nervous system, physical and cognitive impairments and disabilities often abate. These gains may be partly mediated by mechanisms that allow reorganizing of the structure and function within gray and white matter. The potential to enhance neurologic recovery by manipulating the brain and spinal cord must now be considered in clinical practice. Today's rehabilitation routines may not encourage maximum recovery. Indeed, some commonly used physical and pharmacologic methods could inhibit the restoration of motor activities such as walking. On the other hand, therapies that use our expanding knowledge of neuroplasticity could lead to better results for patients.

(Dobkin BH: Neuroplasticity—Key to recovery after central nervous system injury. West J Med 1993; 159:56-60)

Each year more than half of the 300,000 survivors of stroke, the 100,000 survivors of serious traumatic brain injury, and most of the 10,000 victims of spinal cord injury will have paralysis or impaired motor control that leads to disability. The cardinal goal of early treatment is to prevent or treat complications that add to morbidity and death. New pharmacologic approaches such as the use of high-dose steroids and gangliosides may decrease neuronal and tissue damage after ischemic, hypoxic, and traumatic injury.[1-3] These will become the first step in neurologic restoration. The next step includes inpatient and outpatient physical, occupational, speech, cognitive, psychosocial, and vocational rehabilitation to reduce disability and reintegrate the patients into the community. Because clinical trials in rehabilitation are often not scientifically designed and interventions are poorly defined,[4,5] none of the numerous retrospective and prospective uncontrolled studies of general neurologic rehabilitation nor the few controlled clinical trials that compared types of programs or training techniques have clearly shown efficacy.[6,7] Most rehabilitation specialists, however, believe that most patients improve in function over the 3 to 18 months after injury, even though paresis and sensory and cognitive loss may remain the same. The spontaneous recovery of reversibly injured, edematous, and metabolically depressed tissue, compensatory behavioral training, strong motivation, a supportive milieu, and assistive devices are among the more easily recognizable influences that may account for gains.*

One of the most challenging goals in neurologic rehabilitation is to increase recovery of motor control for walking and for reaching and fine coordinated movements of the upper extremity. Here, too, traditional theories and activities in physical therapy often rest on scientifically unsubstantiated grounds. The potential for some restoration after injury probably lies within the anatomic and physiologic reorganization of the cortical, subcortical, and spinal circuits that control motor output.

Sensorimotor Pathways and Recovery

Increasing evidence from neurophysiologic studies points to numerous parallel systems that cooperate to manage the diverse information necessary for the rapid, precise, and yet highly flexible control of multijoint movements. These circuits might contribute to spontaneous and training-induced recovery of function.

The primate motor cortex has separate clusters of output neurons that can facilitate the same spinal motor neuron. Also, a single cortical motor cell can project to the spinal motoneurons for several muscles, even those that might act across a joint. This overlapping organization contributes to the control of the complex muscle synergies for voluntary movement.[8] These motor and neighboring cortical sensory neurons are sensitive to inputs from the periphery and can adapt in remarkable ways during training. In adult and developing animals and in humans, these representations are capable of much physiologic and perhaps structural reorganization.[9] Merzenich and colleagues showed that the cortical sensory representation of hand skin of primates trained to use that hand spread into the previously mapped area of nearby neurons that had, before training, served the skin that surrounded the stimulated area.[10] Similar cortical representational changes were especially likely to arise during training that involved learning and the acquisition of specific skills.[11]

*See also the editorial by M. E. Selzer, "A Scientific Basis for Neurologic Rehabilitation," on pages 91-92 of this issue.

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Many other lines of research in animals suggest that compensation after a central or peripheral injury can be due to a functional shift to neighboring neurons.[12-14] In humans, cortical sensory reorganization has occurred within four weeks after amputation of an arm.[15] When the patient's face was touched, the patient experienced the sensation in the missing hand, suggesting that the sensory input from the face had invaded the cortical hand area. This plasticity probably arises by the unmasking of previously silent synapses from thalamocortical and intracortical circuits that are mediated by acetylcholine and norepinephrine, but in some instances might arise from the sprouting of dendrites over short distances.[16] Studies by magnetic and electrical cortical stimulation,[17] as well as of regional cerebral blood flow and metabolism by positron emission tomography, also reveal evidence of anatomical and functional reorganization after injury similar to that found in experiments in animals. For example, after a subcortical striatocapsular infarction that produced a right hemiparesis, but from which the patients recovered hand use, finger tapping and right-handed squeezing showed bilateral rather than contralateral activation of cortical motor neurons.[18] Also, regions related to selective attention and intention were activated, which suggests that they must come into play when a movement reorganizes.

The failure to use a weakened upper extremity is common after stroke and head trauma. In studies of both animals and humans, the quality of movements by the involved limb improved simply by not allowing the subject to use the unaffected limb.[19] This forced-use strategy could lead to reaching and grasping that is accomplished by an alternative strategy, such as substituting whole-body movements for the loss of supination and pronation of the arm.[20] Plasticity in behavior presumably has a neural substrate that might include reorganization of cortical representation, increased efficiency of residual pathways, and a greater use of alternate descending pathways. Can rehabilitation specialists incorporate this modulation of cortical centers into treatment strategies? The inherent adaptability offers the possibility that specific training plans and drugs that increase local synaptic activity might augment remodeling and, in turn, improve sensorimotor and higher cognitive functioning.

Descending Pathways

The premotor, supplementary motor, and primary motor cortices exert what Hughlings Jackson (the neurophysiologist who proposed the theory of hierarchic control in the nervous system) called "the least automatic control" over voluntary motor commands. Each area receives a separate and independent set of signals from adjacent and remote regions and sends parallel but separate signals to the brain stem and spinal cord.[21] This schema accounts for some of the nuances of impairments in motor control after a cortical injury, such as difficulty in starting a movement or in controlling bimanual and sequential movements. Other pathways also exert great influence. In primates, cortical, thalamic, limbic, and brainstem signals feed into the basal ganglia and contribute to a motor behavior by direct projections to the midbrain motor region and by indirect projections to the thalamus. The basal ganglia influence motor circuits through their myriad miniloops to help specify the combination, sequence, and direction of movements.[22] These parallel arrangements occur in cerebellar and most other sensory and motor projections.[23]

After an injury, the balance of activities of these networks is reset. The intact, parallel systems from cortical and especially subcortical areas might partially compensate or substitute for injured ones. This might require specific cognitive and motor retraining. For example, skeletal muscle strength was shown to increase by having normal persons imagine that they were contracting a hand muscle.[24] A neural process was postulated for this increase in strength. Positron emission tomographic studies suggest that the strengthening is made possible by the activation of central motor planning areas outside of the primary motor cortex that increase the coordination of outputs to the muscle.[25]

Bilateral Descending Pathways

The primary motor cortex contributes about 40% of the 1 million corticospinal fibers that enter each medullary pyramid. From 70% to 90% of pyramidal fibers decussate into the lateral corticospinal tract, and 10% to 30% remain uncrossed and form the ventral corticospinal tract.[26] Sparing of only 17% of the crossed fibers was enough in one human study to allow clinically useful improvement in hand, finger, and toe function.[27] Axons of the uncrossed ventral tract, as well as from the vestibulospinal and reticulospinal tracts, are especially likely to connect to bilateral spinal motoneurons associated mostly with axial and proximal girdle muscles. Even some of the crossed lateral corticospinal tract fibers will connect within the cord's gray matter with interneurons of the opposite side. Although attempts to demonstrate the actions of residual pyramidal pathways after a brain injury in adults has met with variable success,[28,29] it is likely that some pyramidal and especially nonpyramidal fibers from the brain stem contribute redundancy for motor control. This may account for how persons with hemiplegia regain modest arm function and enough use primarily of their antigravity muscles on the paretic side to advance the legs for walking.

Primitive Centers for Automatic Movements

The brain stem and spinal cord have their own intrinsic centers for locomotion. The descending message to start the process of walking seems to be carried by reticulospinal pathways from specific areas of the midbrain and pons that synapse with lumbar spinal neurons.[30] Electrical stimulation of these regions and cholinergic agonists and excitatory amino acids like glutamate are among the neurotransmitters that cause a decerebrate cat to step when placed on a treadmill. In cats, monkeys, and humans, hemisection of the upper lumbar spinal cord is followed by considerable recovery of locomotion, mediated at least in part by descending reticulospinal fibers on the intact

side that cross at a segmental level below the transection.[31] The use of systemic drugs that increase or block the neurotransmitters of this pathway might enhance or inhibit the ability of patients to step.

While cortical and peripheral sensory input is essential for smooth, normal locomotion, the starting and timing of stepping appears to be primarily the task of a self-oscillating lumbar interneuronal network. Even an isolated section of lumbar spinal cord can produce cyclical outputs that rhythmically flex and extend a joint.[32] The circuits of the lumbar stepping motoneurons are especially influenced by descending serotonergic and noradrenergic pathways from brain-stem nuclei. They set the gain for sensory and motor neuronal activation and modulate both the oscillatory behavior of spinal neurons and specific aspects of the locomotor pattern.[33]

After a complete lower thoracic spinal cord transection, adult cats and other mammals can be trained on a treadmill so that their paralyzed hindlimbs fully support their weight, rhythmically step, and increase their walking speed toward what a normal cat can do.[34] Serotonergic and noradrenergic drugs can enhance the stepping pattern; strychnine, through a glycinergic path, quickly induces it. Additional studies on adult spinal-transected cats that were trained only to stand and then encouraged to step on a moving treadmill showed that postural support alone was detrimental to subsequent locomotion.[35] Thus, the lumbar spinal cord of adult cats, in the absence of supraspinal input but with peripheral sensory input, retains the capability to generate hind-limb stepping. Static physical therapies in cats impede recovery, whereas rhythmic alternating movement of the limbs with joint loading seems critical to the recovery of locomotor output.[36] In other experimental models of spinal cord injury, physical exercise also seems to contribute to the recovery of locomotion. For example, in adult rats who had a three-quarter section of the midthoracic spine that spared only the lateral aspect, those who were allowed to roam freely achieved motor recovery and locomotion and those who were immobilized for three weeks did not.[37] Most physical therapies emphasize standing and static balance early after the start of hemiplegia and paraparesis before a patient proceeds to training in walking. Can rehabilitation specialists make use of these findings in animals and of the intrinsic properties of locomotor centers?

Strategies to Enhance Recovery of Locomotion

Using a protocol similar to treadmill stepping in the thoracic-spinalized cats, several groups have trained subjects with chronic paraplegia to step. As much as 50% of their body weight was suspended in a harness connected to an overhead hydraulic lift. Therapists manually assisted their legs so that they could step on a slowly moving treadmill belt. The aim was to gradually achieve full weight-bearing at increasing treadmill velocities. In at least 20 patients who probably had some residual descending neural input but who had been able to walk little or not at all, independent treadmill walking was achieved and the subjects became able to walk overground.[38-40] In addition, in subjects with complete thoracic spinal cord injuries, rhythmical flexor and extensor electromyographic activity can develop in their paralyzed leg muscles during assisted stepping with body weight-supported treadmill training, but they cannot step independently.[41] Greater sensory input such as increased loading of the joints and cutaneous electrical stimulation that was timed to the gait cycle enhanced this effect and could evoke hip flexion. Serotonergic and noradrenergic drugs also altered motor output.[42] When this training strategy was applied to six patients with chronic hemiplegia, treadmill and overground velocity increased.[43] These findings offer yet another mechanism for gains in walking after a brain or spinal injury. More important, they suggest new physical and pharmacologic strategies that can influence residual descending cortical and subcortical pathways and spinal circuits to enhance the ability to walk.

Neurotransmitter Effects on Recovery

Studies in animals and a small clinical trial have provided preliminary evidence that a variety of pharmacologic agents might increase or decrease the rate or degree of recovery of sensorimotor function and walking after a cerebral injury. After being given dextroamphetamine, rats and cats that underwent a unilateral or bilateral ablation of the sensorimotor or frontal cortex had more rapid recovery of the ability to walk across a beam than did controls. This endured well past the single or intermittent dosing schedule of the drug.[44] The use of amphetamine also seemed to work in a small group of patients shortly after they had a stroke, though these results have not been replicated.[45] In both instances, the drug worked only when combined with physical activity and practice, the equivalent of training and motor experience. The dopamine blocker, haloperidol, prevented this recovery in the animals. Investigators have speculated that noradrenergic drugs might alleviate a functional depression in remote, transsynaptically connected regions of the brain.[46] Such physiologic inactivity of intact neurons, called diaschisis, is revealed by positron emission tomography as regions of hypometabolism.

Other neurotransmitters, including acetylcholine, norepinephrine, dopamine, γ-aminobutyric acid, and serotonin, have enhanced motor recovery whereas phenytoin, scopolamine, clonidine, neuroleptics, and benzodiazepines have slowed gains in specific experimental designs. Benzodiazepines have also been associated with poorer and slower 30-day recovery of sensorimotor function in patients with a stroke.[47] It is not surprising that some drugs could improve one function but be associated with another type of motor or cognitive dysfunction.[48] Some drugs have more clear-cut mechanisms of action. For example, the conduction of action potentials along demyelinated axons could be restored by pharmacologic agents like 4-aminopyridine, which blocks potassium channels and improves impulse conduction.[49]

Drug studies in humans are complicated. The type, location, extent, and age of the lesion; the specific drug, its

dosage, time of initiation, duration of use, and adverse effects; and the accompanying physical or cognitive therapy that might add to a drug's effect must be determined. It is clear that clinicians must select medications with special care in the months after a cerebral injury and monitor for effects that seem to speed or impede recovery.

Biologic Mechanisms of Restoration

Motor learning can produce the arborization of dendrites and the growth of synapses in the cerebral and cerebellar cortex in animals.[50,51] After a unilateral injury to the sensorimotor cortex serving the forelimb of adult rats, one study showed the growth of neuronal dendrites in the sensorimotor cortex of the normal opposite side. This was associated with early disuse of the impaired forelimb and an increased use of the normal forelimb as it compensated for the paretic one.[52] As the paretic limb improved, the increased dendritic growth of the uninjured cortex was pruned back in parallel with less demand for its use.

We can begin to imagine how a combination of neurobiologic measures might increase connections and perhaps allow axons to regenerate. This research is especially applicable to spinal cord injury because less than 10% of residual supraspinal input seems needed to recover the ability to walk.[53,54] To regain even one more level of useful upper extremity function, even to go from a C-5 to a C-6 quadriplegia, would greatly add to a patient's independence.

Possible Therapies From Molecular Biology and Biotechnology

Tissue culture and vertebrate models have shown that substances in the extracellular matrix tend to inhibit axonal elongation at the site of injury. Peripheral nerve[55] and fetal tissue transplants[56] have been used with some success to bridge areas of spinal gliosis. Antibodies have been directed against molecules on glial cells that block neuritic extension.[57] Neurotrophic growth factors have been used to protect neurons and to signal neuronal machinery to make the substances necessary for extension. Direct transplantation of motor neurons and cells that produce a specific neurotransmitter to replace lost noradrenergic projections has met with some success.[58,59]

The techniques to manipulate the promoters and inhibitors of neuroplasticity are still in early development. As with the other possible mechanisms for neurologic restoration, their effectiveness will depend in part on strategies developed by rehabilitation specialists to boost activity along neural circuits.

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Evaluating Chest Pain in the Emergency Department

Discussant
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This discussion was selected from the Grand Rounds in the Department of Medicine, University of New Mexico School of Medicine, Albuquerque.

Chest pain is one of the most difficult diagnostic problems for physicians working in an emergency department. In this setting, more malpractice dollars are awarded for missed myocardial infarction than for any other physician error. This problem usually occurs when the patient has atypical symptoms, the physician is inexperienced, or the diagnosis is not considered. The clinical manifestations of myocardial infarction vary greatly, and patients with "atypical" presentations have a poorer prognosis than those with classic symptoms. Although no feature of a patient's history excludes infarction with certainty, pain that is sharp, positional, pleuritic, or reproduced by palpation indicates a lower probability of acute ischemic heart disease. New immunochemical methods and serial sampling strategies have increased the sensitivity of creatine kinase-MB as an indicator for the disorder. Recent investigations have also established the prognostic value of the initial electrocardiogram. These methods allow emergency physicians to assess the risk of complications and to perform triage when there is a shortage of beds in the coronary care unit. Emergency physicians must also consider other diseases for which coronary care might be beneficial.

(Murata GH: Evaluating chest pain in the emergency department. West J Med 1993; 159:61-68)

GLEN H. MURATA, MD*: Chest pain is one of the most frustrating problems for physicians working in an emergency department. The diagnostic possibilities range from a life-threatening event, such as acute myocardial infarction, to a process as trivial as muscle strain. Because it is impossible to exclude the diagnosis of myocardial infarction with certainty, physicians are often forced to admit patients who do not benefit from coronary care. They also face ethical and legal problems. Although admitting a patient lowers the risk of a malpractice claim, it also increases hospital costs, reduces the availability of monitored beds, increases the workload of house staff, and increases the anxiety of patients with benign disorders.

Five years ago, I reviewed studies concerning the cost-effectiveness of coronary care units (CCUs) for patients with chest pain.[1] I did not examine ways of identifying which patients should be admitted to hospital or assessing their risk of complications. Recent studies have provided new insight into the roles of patients' history, serum enzyme levels, and the electrocardiogram (ECG) in the assessment of patients with suspected myocardial ischemia. In this discussion I summarize these findings. Although they improve the admission practices of emergency physicians, multivariate prediction models for ischemic heart disease[2-7] are beyond the scope of this review.

I will address six questions: Why is chest pain such a frustrating problem for emergency physicians? Is there a "typical" presentation for myocardial infarction? What qualities distinguish a myocardial infarction from other causes of chest pain? Should serum creatine kinase levels be measured in patients seen in emergency departments for chest pain? How useful is the initial ECG? And, finally, should patients with crescendo angina be admitted to the hospital?

Why Is Chest Pain Such a Frustrating Problem?

Patients with chest pain represent a considerable legal risk for physicians working in an emergency department. In this setting, more malpractice dollars are awarded for missed myocardial infarctions than for any other physician error.[8] Between 1974 and 1985, these losses amounted to $5.3 million, or nearly 20% of the total amount awarded for emergency care. Lee and co-workers showed that the prognosis was poor for patients with infarction mistakenly discharged from the emergency departments of six hospitals.[9] In their study, 35 patients were compared with 105 patients with myocardial infarction admitted through the emergency department. Patients whose infarctions were missed were younger and less likely to have chest pressure or diaphoresis, a history of

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ABBREVIATIONS USED IN TEXT

CCU = coronary care unit
CK = creatine kinase
ECG = electrocardiogram
LR = likelihood ratio
ROC = receiver operating characteristic

an infarct, or ischemic changes on the initial ECG. Nine of these patients (26%) died within 72 hours, a mortality substantially higher than for those admitted to hospital. Rusnak and colleagues examined the characteristics of emergency physicians who missed myocardial infarctions.[8] Cases were found by searching the files of two malpractice insurance companies. The study compared 65 missed cases with 65 control patients in whom an infarct was correctly diagnosed. Again, patients with missed infarctions were younger, more likely to have atypical complaints, and less likely to have ECGs diagnostic of myocardial infarct. Physicians who missed this disorder gave less detailed descriptions of chest pain, did not review cardiac risk factors as often, were less likely to record heart and lung examinations, and obtained ECGs less often. They also had considerably less emergency department experience.

A way of avoiding this problem is to admit patients to the hospital even if they are at low risk for myocardial infarction. Fineberg and associates showed, however, that this strategy is not feasible.[10] They analyzed the cost-effectiveness of admitting patients with a 5% probability of an infarct to a CCU. They assumed that the risk of ventricular fibrillation was 4.5% and that this risk was reduced by 90% in the CCU; these estimates were based on observations made during clinical trials of lidocaine prophylaxis. They also assumed that the baseline risk for heart block was 2.3% and that coronary care reduces the mortality of this complication from 52% to 34%. Hospital costs were expressed in 1980 dollars. These investigators found that admitting a low-risk patient to the CCU would have increased costs by $1.26 million per life saved and $113,000 per year of life saved compared to a program of home care and outpatient follow-up.

Thus, although a missed diagnosis of myocardial infarction carries an exceptionally poor prognosis and increases the risk of a malpractice suit, it is not cost-effective to admit every patient with chest pain to the CCU. Ideally, the decision to admit a patient with "atypical" features should be made by a physician with experience in evaluating such patients.

Is There a 'Typical' Presentation for Myocardial Infarction?

Although the terms "typical" and "atypical" are commonly used by physicians for different patterns of chest pain, there is little justification for their use. Numerous pathologic, epidemiologic, and clinical studies have shown that many patients with myocardial infarct do not have the chest pain that is conventionally attributed to a cardiac origin. Two autopsy series showed that many patients dying of the disorder in hospital are not suspected of having a coronary event.[11,12] Zarling and colleagues examined 100 consecutive, autopsy-proven cases of acute myocardial infarction and found that an antemortem diagnosis was made in only 53. Of the 47 unsuspected cases, 29 (62%) had no suggestive history and 27 (57%) had nondiagnostic or insufficient laboratory tests. Similar conclusions were reached by Goldman and associates.[12] They found that 32% of infarcts confirmed at autopsy were not suspected before death. Among major diseases, myocardial infarction was second only to pulmonary embolism in the rate of missed diagnoses.

Epidemiologic studies have shown that a large proportion of patients with ECG evidence of infarct have had coronary events that were clinically inapparent. Kannel and co-workers, summarizing the results of the Framingham study, found that 26% of infarcts in men and 34% in women were unrecognized.[13] Half of the infarctions were silent, and the other half were associated with symptoms so atypical of the disorder that the diagnosis was not suspected by the patient or the physician. The proportion of unrecognized infarctions increased with age in men but not in women. Hypertension was the most common predisposing factor in this study. Diabetes mellitus increased the likelihood of an unrecognized event in men but had the opposite effect in women. Kannel and associates pointed out that the rate of unrecognized myocardial infarcts is underestimated by surveillance studies because 10% of anterior and 25% of inferior infarcts lose their characteristic ECG pattern within two years.[13]

These findings were confirmed by several other studies.[14-17] The Western Collaborative Group found that 29.8% of myocardial infarcts in a cohort of 3,182 initially healthy adults were unrecognized.[14] In a study at Tel Aviv University, Medalie and Goldbourt observed 9,509 subjects for five years and discovered that 39.8% of all infarcts were not recognized.[15] In the Multiple Risk Factor Intervention Trial (MRFIT), 281 participants had a physician's diagnosis of definite infarction without serial ECG changes, 179 had an infarct with ECG changes, and 157 (25.4%) had serial ECG changes suggestive of an infarct without symptoms.[16] Asymptomatic infarction accounted for 33% of transmural infarcts in the Honolulu Heart Program.[17] That study showed that coronary mortality for patients with silent infarcts was 1.5 times greater than for patients with recognized infarctions, although the difference was not significant. Thus, the discovery of pathologic Q waves on an ECG justifies a cardiac evaluation, even if that finding is incidental.

Other studies have found that some patients with symptomatic infarction do not have chest pain. Uretsky and co-workers showed that 26 of 102 patients with acute infarction had other chief complaints: 14 (54%) had dyspnea, 5 (19%) had abdominal pain, and 4 (15%) had fatigue.[18] Patients without pain were older, had a lower prevalence of angina, and were less likely to smoke. The mortality of those without pain (50%) was much higher than for those with pain (18%).

In summary, many cases of fatal myocardial infarct

are not suspected before death, a large proportion of patients with ECG evidence of infarct have no suggestive symptoms, and many of those with symptoms have no chest pain. These studies do not support the concept that there is a presentation typical of myocardial infarction.

What Distinguishes Myocardial Infarction From Other Causes of Chest Pain?

One way to understand which characteristics distinguish a myocardial infarct from other causes of chest pain is to assemble two groups of patients—one with infarct and the other without—and compare their clinical features. There are several methodologic problems with this type of study, however. It is often difficult to confirm that a person has had a myocardial infarct. Moreover, a "workup bias" can occur for studies done in the outpatient setting. This bias occurs because patients thought not to have an infarct are discharged from the emergency department, which makes their infarcts more difficult to detect. The apparent lack of association between atypical features and myocardial infarction is therefore the result of a self-fulfilling prophecy. Finally, noncardiac chest pain represents a spectrum of disorders that can vary from hospital to hospital. A symptom that distinguishes cardiac from noncardiac pain at one facility may have no value at another. External validity can be strengthened by providing a detailed description of the diseases afflicting the noncardiac group, but it is difficult to find a study in which the cause of noncardiac pain has been thoroughly investigated.

Two studies have been published in which careful attention has been paid to these problems. Lee and colleagues examined the quality of chest pain in 596 patients seen in an emergency department, 317 of whom were admitted to the hospital and 279 of whom were released.[19] Nonadmitted patients returned within 48 to 72 hours for repeat measurements of cardiac enzymes and an ECG. A final diagnosis of myocardial infarction was made in 17% of all subjects. Myocardial infarct was uncommon if chest wall palpation fully reproduced the chest pain, if the pain was completely pleuritic, or if it was brought on only by changes in position or movement. Pain that was partially pleuritic, positional, or reproduced by palpation was seen, however, in a considerable number of the patients with an infarct. The lowest-risk group had a combination of three findings: sharp or stabbing pain, no history of angina or myocardial infarction, and pain that was reproduced by chest wall palpation or that had a pleuritic or positional component. None of the 48 patients in this group had a myocardial infarct or unstable angina.

In Table 1, I have pooled some of these data and calculated likelihood ratios (LR) for different types of chest pain. From probability theory, it can be shown that

$$\text{posttest odds of MI} = \text{pretest odds of MI} \times \text{LR}$$

where MI refers to myocardial infarct and the LR is defined by the expression:

$$\text{LR} = \frac{\text{probability of the observation in patients with MI}}{\text{probability of the observation in patients without MI}}$$

An observation with an LR of less than 1 reduces the odds that a patient has an infarct, and an observation with an LR of greater than 1 increases the odds. For example, suppose the initial probability of a myocardial infarct is 0.15, the mean prevalence reported from emergency departments of several institutions.[1] An observation with an LR of 0.2 will reduce the probability to about 3%. Note that LRs vary widely for the different types of chest pain. Features that might be considered atypical have LRs of about 0.2, suggesting that they cannot be used to exclude an infarct with certainty.

Davies and associates published an interesting study in which extraordinary effort was made to establish the diagnosis in a group of patients admitted to hospital with noncardiac chest pain.[20] They compared 52 patients with ischemic heart disease with 18 patients with esophageal disease documented by acid perfusion tests, esophageal manometry, cine barium swallows, or endoscopy with biopsy (Table 2). Pain radiating to the left arm, provoked by exercise, relieved by rest or nitroglycerin, or of a crescendo pattern did not distinguish cardiac from esophageal pain. On the other hand, pain persisting as an ache for hours; provoked by swallowing, recumbency, or stooping; or relieved by antacids was significantly more frequent in the group with esophageal disease.

Two important points should be made about this study. First, the patients with esophageal disease may have been admitted because their pain was suggestive of myocardial ischemia. A selection bias could therefore ex-

TABLE 1—*Comparison of Chest Pain Quality in Patients With and Without Myocardial Infarction (MI)**

	MI Patients, n=104		*Non-MI Patients, n=349*		
Chest Pain Quality	*No.*	*(%)*	*No.*	*(%)*	*Likelihood Ratio*
Pressure	61	(59)	116	(33)	1.8
Aching	10	(10)	54	(15)	0.67
Burning or indigestion	10	(10)	24	(7)	1.4
Sharp or stabbing	8	(8)	122	(35)	0.23
Partially or completely reproduced by palpation	8	(8)	141	(40)	0.20
Partially or completely pleuritic	6	(6)	119	(34)	0.18
Partially or completely positional	11	(11)	114	(33)	0.33
Fully reproduced by chest palpation, pleuritic, or evoked by changes in position or movement	7	(7)	138	(40)	0.18

*From Lee et al.[19] Patients with unstable angina have been excluded. Certain categories have been pooled because of small sample sizes.

TABLE 2—*Differentiation of Ischemic Cardiac and Esophageal Pain**

Characteristics of Pain	Cardiac Pain, n=52 No.	(%)	Esophageal Pain, n=18 No.	(%)
Location				
Retrosternal	51	(98)	18	(100)
Lateral radiation	36	(69)	2	(11)
Radiation to left arm	20	(38)	6	(33)
Pattern of attacks				
Persists as ache for hours	13	(25)	14	(78)
Nocturnal awakening	13	(25)	11	(61)
Crescendo pattern	16	(31)	7	(39)
Provoked by				
Emotion	15	(29)	7	(39)
Swallowing	3	(6)	7	(39)
Recumbency or stooping	10	(19)	11	(61)
Exercise	38	(73)	12	(67)
Variable threshold	5	(10)	7	(39)
Develops 10 minutes after exercise stops	2	(4)	6	(33)
Relieved by				
Rest	32	(62)	9	(50)
Antacid	5	(10)	8	(44)
Nitroglycerin	32	(62)	10	(56)

*From Davies et al.[20]

plain the lack of diagnostic value for certain types of pain. The study does imply that hospital-based physicians should ask more specific questions about the pattern of attacks or provocative factors if they are to make important contributions to the evaluation done in the emergency department. Second, of 30 patients without cardiac or esophageal pain, 40% had a major disease involving a visceral organ. This finding suggests that patients admitted to the hospital with chest pain should be evaluated for other diseases if myocardial infarction has been ruled out.

Two other historical items might be of use for the assessment of patients with chest pain. Fesmire and Wears examined the prognosis of 422 patients admitted to the hospital with suspected infarct.[21] Compared with those whose pain had resolved before entry, patients with persistent or recurrent pain in the emergency department had 2.3 times the risk of interventions, 1.7 times the risk of all complications, 3.8 times the risk of life-threatening complications, and 2.4 times the risk of an acute infarct. An even poorer prognosis was found for patients with suspected infarction who had never experienced pain. Ingram and co-workers studied the importance of vomiting in patients with acute ischemic cardiac disease.[22] Vomiting occurred in 25 of 58 patients with transmural infarctions but only 1 of 51 with unstable angina or subendocardial necrosis. The investigators concluded that, when vomiting occurs with acute ischemic heart disease, a transmural infarction should be expected 90% of the time. The time of the start of chest pain does not appear to have much diagnostic value. Although cardiac pain tends to occur within an hour of awakening,[23] noncardiac pain also occurs more frequently during the morning hours.[24]

Should Serum Creatine Kinase Levels Be Measured in Patients in Emergency Departments With Chest Pain?

The introduction of rapid, inexpensive, and accurate methods for measuring serum creatine kinase (CK) levels has greatly facilitated the evaluation of patients with suspected myocardial infarction. Creatine kinase is an enzyme that catalyzes the transfer of phosphate from creatine phosphate to adenosine diphosphate. It comprises two enzymatically active subunits, the M and B types. The BB isoenzyme, which has the fastest electrophoretic mobility, occurs predominantly in brain tissue. The MM type is the isoenzyme found in skeletal muscle, although sensitive laboratory methods have shown that skeletal muscle has trace amounts of MB as well. Cardiac CK is composed of 85% MM and 15% MB. During embryogenesis, BB appears first in skeletal muscle, then MB, and finally MM. During skeletal muscle regeneration, the same process may occur. Thus, cardiac muscle is the only important source of serum CK-MB except in patients with myopathies such as muscular dystrophy or polymyositis.[25-27]

Routine assays of CK do not measure the quantity of enzyme. Instead, they estimate CK concentration by determining its enzymatic activity. Separation of the isoenzyme activities is usually done by a physical separation technique such as electrophoresis or ion-exchange column chromatography. Newer assays of CK-MB rely on immunologic methods and measure enzymatic mass. A popular procedure consists of a double-antibody "sandwich" technique. Separation is done by exposing specimens to anti-B antibodies bound to a solid phase and washing away unbound enzyme. The solid phase is then exposed to anti-M antibodies linked to an indicator enzyme such as alkaline phosphatase. A substrate solution is added and the amount of solid-phase activity measured.

Before reviewing studies of CK levels in patients with myocardial infarction, it is necessary to examine the sources of bias that could affect a study evaluating a diagnostic test.[28] Several questions should be asked: Has the test been studied in a patient sample with an appropriate spectrum for the disease in question? Has the test been interpreted by a person blinded to the diagnosis? Has the diagnosis been made by a person blinded to the test result? And, finally, has the study avoided "incorporation bias"? This bias occurs when the test undergoing evaluation is actually used to make the diagnosis.

Unfortunately, many studies of CK levels in patients with suspected infarcts have been flawed by these biases. Almost all have been done in patients with chest pain. Whether these measurements are useful in patients with other presentations is unknown. Other problems result from the lack of a "gold standard" for diagnosing myocardial infarct because neither autopsy nor noninvasive methods are completely satisfactory ways of confirming the diagnosis. Many studies evaluating the diagnostic efficacy of CK activity for myocardial infarct used enzyme changes to establish the diagnosis—an example of incorporation bias. Investigations of CK activity in pa-

tients with chest pain should therefore be interpreted with caution.

Lee and associates studied the efficacy of two diagnostic strategies for 639 patients with chest pain presenting to an emergency department.[29] Strategy A involved measuring total CK activity in a single specimen; strategy B involved measuring CK-MB levels if the total CK level was elevated. Serum CK-MB activity was determined by ion-exchange chromatography. The diagnosis of myocardial infarction was made by enzyme changes, ECG criteria, technetium Tc 99m scanning, or unexplained sudden death within 72 hours. Myocardial infarction was diagnosed in 26% of admitted and 2% of nonadmitted patients. Elevated total CK levels were found in 38% of patients with and 20% of patients without myocardial infarcts. Abnormal total CK levels were found in only 25% of patients with infarction within four hours of the start of pain but in 55% of patients presenting after four hours. Elevations of total CK and CK-MB levels were found in 34% of patients with infarcts and only 12% of those without. Again, specimens taken within four hours of the onset of pain showed normal levels in most patients with myocardial infarcts. Analysis of receiver operating characteristic (ROC) curves showed that strategy B was significantly better than strategy A when specimens were taken more than four hours after the onset of pain. The authors concluded that their assays of total CK and CK-MB activity were not sensitive enough to be used as the sole criterion for hospital admission.

Dufour and colleagues evaluated the effectiveness of serial changes in CK activity for 1,214 patients admitted to a Veterans Affairs Medical Center with suspected myocardial infarcts.[30] Specimens were taken at admission and eight hours later, and the value of the first specimen was subtracted from that of the second (Δ-CK). Myocardial infarction was diagnosed in 18% of the subjects. Initial CK levels were normal in 76% of patients with and 85% of patients without infarction. For those with a normal initial value, the Δ-CK was positive in 98% of those with myocardial infarction but in only 16% of those without the disorder. For patients with initially elevated CK levels, the Δ-CK was of no value.

Leung and associates examined CK criteria for diagnosing myocardial infarction in 310 patients admitted to hospital, 151 of whom had an infarct.[31] Three tests were evaluated by ROC and LR analyses: total CK activity, absolute CK-MB activity, and CK-MB activity as a percentage of total CK activity. Specimens were taken every 6 hours for 48 hours. Total CK activity had almost no diagnostic value within six hours of presentation but improved with time. Absolute CK-MB activity was the best test for all time periods.

Quale and co-workers showed that serial measurements of cardiac enzyme activities could be used to determine the risk of infarction for 96 patients admitted to Kings County Hospital (Brooklyn, New York) with unstable angina.[32] Patients with ST-segment elevation on their ECGs were excluded. Myocardial infarction was diagnosed in 19 patients. The initial enzyme activities were higher in the group having infarction, but the predictive value for elevations in any of the serum enzyme levels was low. A second enzyme determination done 6 to 12 hours after admission allowed the separation of high- and low-risk patients. Of 52 patients with two normal CK levels, only 1 had a myocardial infarct, but 18 of 38 with at least one elevated value had infarction.

Three studies suggest that newer immunochemical methods will greatly improve the usefulness of CK measurements in emergency departments.[33-35] Gibler and colleagues examined the diagnostic efficacy of four immunochemical methods for measuring CK-MB levels in 183 patients admitted to hospital with chest pain.[33] Myocardial infarction was documented in 17% by standard enzymatic and ECG criteria. For specimens taken at entry, the immunochemical methods had a sensitivity of 50% to 62.1%, whereas the electrophoretic method had a sensitivity of only 34.5%. At three hours after entry, the newer methods were 92% to 96.7% sensitive and 83% to 96.4% specific. The standard method had a three-hour sensitivity of 76.9% and a specificity of 98.6%. Mair and associates evaluated the performance of an immunoenzymometric assay for CK-MB mass.[34] In 36 patients with myocardial infarction presenting within four hours of the start of chest pain, CK-MB mass increased an hour earlier than CK and CK-MB activity. In 126 patients seen in an emergency department with chest pain, CK-MB mass had a significantly higher sensitivity, positive predictive value, and likelihood ratio than CK and CK-MB activities.

Gibler and co-workers reported the results of a multicenter study of an innovative strategy for the early identification of myocardial infarct in patients admitted with chest pain.[35] They used a rapid, two-site immunoenzymatic assay of CK-MB on specimens drawn at entry into the emergency department and one, two, and three hours later. The sequence was considered "positive" if results were abnormal for any of the four specimens and "negative" if all four were normal. Of 69 patients with infarction with nondiagnostic ECGs, 55 had a positive result (sensitivity 79.7%). The specificity of the testing sequence was 93.7%. The combination of serial CK-MB measurements and the findings of the initial ECG detected 88.4% of patients ultimately given the diagnosis of myocardial infarction. Unfortunately, the strategy was not evaluated in patients discharged from the emergency department.

Thus, standard methods for measuring CK and CK-MB activity are not sensitive enough to be used as a screening test for myocardial infarction, particularly if the patient presents within four hours of the onset of pain. Newer immunochemical methods and sampling strategies have greatly increased the sensitivity of CK-MB measurements for diagnosing the disorder.

How Useful Is the Initial ECG?

Sensitivity and Specificity

Although the ECG has been a standard part of the cardiac evaluation for decades, new investigations have re-

defined its role in the management of patients with chest pain. The ECG is suggestive of myocardial infarction in only half of patients at presentation.[11,36,37] In a study by Zarling and associates, of 100 autopsy-proven cases, 85 had ECGs available for review.[11] They were diagnostic of infarction in 29%, suggestive in 32%, nonspecific in 26%, and unchanged in 13%. Rude and colleagues reported on the frequency of abnormal ECGs in 3,697 patients admitted to the CCUs of five university hospitals with chest pain of greater than 30 minutes' duration.[36] Electrocardiograms were considered positive for myocardial infarct if there were new Q waves, new ST-segment elevations or depressions of 0.1 mV or more, or complete left bundle branch block. With these criteria, the ECG had a sensitivity of 81%, a specificity of 69%, and a predictive value of 72%. McGuinness and co-workers studied 918 patients admitted to a CCU over two years.[37] Only half of the cases of infarction were diagnosed from the initial ECG.

Despite the poor sensitivity for diagnosing infarction, the ECG has become the standard method of selecting patients for thrombolytic therapy. Lee and associates examined the clinical implications of true- and false-positive ECGs in 7,734 patients seen in emergency departments with chest pain.[38] Myocardial infarction was eventually diagnosed in 14% by enzyme elevations, ECG changes, technetium scanning, or unexplained sudden death. "Positive" ECGs were found in 461 patients with and 144 without infarction—a predictive value of 76%. Only 261 patients (23%) with infarction were younger than 75 years, presented within four hours of the beginning of pain, and had ECGs showing probable acute myocardial infarction; 60 patients without infarction also fulfilled these criteria. Thus, for every eight patients correctly selected for thrombolytic therapy, two were selected incorrectly.

Prognostic Value of the Initial ECG

Several studies have defined the prognostic value of a normal initial ECG. In a study by Lee and associates of emergency department patients with chest pain, only 1 (0.9%) of 114 patients with a normal ECG had an infarct.[19] Slater and colleagues studied the outcome of 775 patients admitted to a CCU.[39] Myocardial infarction evolved in 10% of those with normal ECG findings and 8% with minimal changes. Only 1% of patients with a normal ECG and 6% of those with nonspecific findings had a complication for which CCU interventions were potentially beneficial. Karlson and associates found that, of 4,690 patients admitted to a hospital for a suspected infarct, 1,576 (34%) had a normal admission ECG[40]; infarct developed in only 90 (6%). Each patient was also assigned to one of four categories according to the level of suspicion for an infarct. For those with no suspicion (n = 466), only 6 (1.3%) had a myocardial infarction.

Brush and co-workers showed that the initial ECG could be used to predict complications in 469 patients admitted to the hospital with chest pain.[41] The initial ECG was considered "positive" if it showed pathologic Q waves, ST-segment elevation, ST-segment depression, or T-wave inversion consistent with infarction, ischemia, or strain; left ventricular hypertrophy; left bundle branch block; or a paced rhythm. Of the 302 patients with a positive ECG, a life-threatening complication developed in 42 (14%) compared with only 1 of 167 (0.6%) with a "negative" ECG. Other complications were 3 to 10 times more likely, interventions 4 to 10 times more likely, and death 17 times more likely if the initial ECG was "positive." These findings were subsequently confirmed by others.[42,43]

Fesmire and associates modified the strategy used by Brush and co-workers by classifying ECGs as positive, normal, or abnormal.[44] An ECG was considered positive if it met that study's criteria. The normal category included ECGs with sinus bradycardia, sinus tachycardia, atrial premature contractions, and occasional ventricular premature contractions. An ECG was classified as abnormal if it did not qualify for the other two categories or if it was positive and unchanged from a previous tracing. Unlike Brush and colleagues, these investigators studied all patients with a suspected infarction, regardless of whether they had chest pain. They found that patients with positive ECGs were at much greater risk for life-threatening complications, interventions, and death than patients in the other two categories. Moreover, those with abnormal ECGs were more likely to require interventions and to die than those whose ECGs were normal.

Other ECG patterns have been shown to be of prognostic value.[45,46] Selarovsky and co-workers evaluated 32 patients with chest pain and ST-segment depressions in the precordial leads and found that 21 had positive T-wave deflections and 11 had negative T-wave deflections. Although the incidence of myocardial infarction was similar for the two groups, hospital mortality was much higher for the patients with negative T-wave deflections. Left main coronary artery disease was also more prevalent in this group. Cohen and associates showed that the number of leads with ST-segment deviation is an important determinant of prognosis.[46] In their study, 90 patients were admitted to hospital with chest pain at rest consistent with either unstable angina or non–Q-wave infarction. An entry ECG with two or more leads showing 1 mm or more of ST-segment deviation was 79% predictive of an unfavorable event. The number of leads with ST-segment deviation correlated with the amount of myocardium in jeopardy as assessed by cardiac catheterization.

Two studies have shown that it is important to compare the current ECG with a previous one.[47,48] Fesmire and associates compared the initial ECG with the most recent one for 258 patients admitted to hospital for a suspected infarct.[47] Again, ECGs were classified as positive or negative according to the criteria of Brush and colleagues.[41] Electrocardiograms were also categorized as changed or unchanged from a previous one. A positive initial ECG that had changed from the previous one was associated with twice the risk of interventions, 2.6 times the risk of complications, 4.2 times the risk of life-threatening com-

plications, and 6.6 times the risk of acute myocardial infarction compared with all other ECG categories. Patients with a negative ECG that had changed from a previous one were twice as likely to receive an intervention as those with unchanged negative ECGs. Lee and co-workers showed that a previous ECG improved the diagnostic accuracy of emergency department physicians for 5,673 adults presenting with chest pain.[48] The admission rates for patients with an infarct with and without previous ECGs were similar. Patients not having an infarct were more likely to avoid CCU admission if a previous ECG was available. The effect of a previous ECG was most notable when the initial ECG findings were consistent with infarction and ischemia. Patients without an infarct and with initial ECGs suggestive of ischemia were twice as likely to avoid being admitted to hospital if a previous ECG was available.

Thus, the initial ECG is not sensitive for diagnosing myocardial infarction but remains the only method for selecting patients for thrombolytic therapy. The ECG is an excellent method of stratifying patients according to the risk of cardiovascular complications.

Should Patients With Unstable Angina Be Admitted to the Hospital?

Crescendo angina poses a special problem for emergency physicians. This diagnosis should be considered for any patient with progressive myocardial ischemia in the absence of an infarct. Because initial laboratory tests are insensitive for infarction, emergency physicians may not be able to distinguish between these two conditions at the time of presentation.

Nattel and colleagues analyzed the outcome of 100 patients admitted to the CCU with increasing frequency, severity, or duration of chest pain.[49] No patient had ST-segment elevation on the initial ECG. Myocardial infarction was documented in 20 patients, ventricular tachycardia in 16, and ventricular fibrillation in 1. Patients with episodes of chest pain lasting more than 30 minutes in the preceding 24 hours, ischemic changes on an ECG, and diaphoresis had a higher frequency of myocardial infarct than those without these features. All patients with ventricular tachyarrhythmias had prolonged chest pain and ischemic ECG changes. Strategies for predicting infarct among these patients were sensitive but not specific.

Several other studies have shown that the prognosis is poor for patients admitted to the hospital for unstable angina, even when an infarct is ruled out in the first 48 hours.[50-52] Heng and colleagues found that in 13% of their patients, an infarct developed between 48 hours and 3 weeks and that the hospital mortality rate was 4%.[50] The long-term mortality was 5% per year. Krauss and co-workers reported a somewhat better prognosis for 100 patients with acute coronary insufficiency and no evidence of infarction in the first 48 hours.[51] Of these, 36 continued to experience ischemic pain after 12 hours, and 6 progressed to infarction later in the hospital course. Fesmire and associates examined the in-hospital prognosis of 131 patients with the discharge diagnosis of angina.[52] In all, 37% required an intervention, 32% had a complication, 5% had a life-threatening complication, and 2% died. These observations suggest that ruling out a myocardial infarct is not an appropriate end point for evaluating patients seen in an emergency department with chest pain. Emergency physicians should regard progressive myocardial ischemia as potentially lethal, regardless of whether an infarct has already occurred.

Summary

Chest pain is a difficult management problem for emergency physicians. The clinical manifestations of myocardial infarction vary widely, and the prognosis is worse for patients whose presentations are atypical. For most patients, neither the history nor laboratory tests can be used to exclude the possibility of infarction. Moreover, patients with crescendo angina are at risk for cardiovascular complications and death. These observations suggest that it is neither feasible nor sufficient for emergency physicians to rule out an infarct. Recent studies have firmly established the prognostic value of the history and ECG. Newer assays and sampling strategies have increased the sensitivity of measuring CK-MB activity as a predictor of myocardial infarction. Physicians should use these methods to assess the risk of complications in patients with chest pain to assure they receive the proper care.

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Epitomes

Important Advances in Clinical Medicine

Otolaryngology—Head and Neck Surgery

The Council on Scientific Affairs of the California Medical Association presents the following inventory of items of progress in otolaryngology–head and neck surgery. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome, and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, researchers, and scholars to stay abreast of these items of progress in otolaryngology–head and neck surgery that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Otolaryngology–Head and Neck Surgery of the California Medical Association, and the summaries were prepared under its direction.

Reprint requests to Division of Scientific and Educational Activities,
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Magnetic Resonance Imaging-Guided Needle Biopsy of Head and Neck Lesions

FINE-NEEDLE ASPIRATION of inaccessible and deep-seated lesions of the head and neck may be difficult to do. If a definite diagnosis can be obtained by aspiration, however, an open surgical biopsy of the lesion and its associated risks can be avoided. Although superficial lesions may be aspirated under the guidance of direct palpation, fine-needle aspiration of inaccessible lesions requires imaging guidance.

Computed tomography (CT) has previously been most useful in guiding the aspiration of nonpalpable lesions. But because magnetic resonance imaging (MRI) is replacing CT as the imaging study of choice to evaluate many areas of the head and neck, the ability to do MRI-directed aspiration for cytologic examination is becoming increasingly important. Magnetic resonance imaging-guided needle placement offers advantages over CT guidance of better soft tissue contrast resolution and the ability to locate lesions inapparent on CT images. In addition, the oblique imaging planes of MRI provide better visualization of the needle tract. Computed tomographic images are limited to the axial plane, making needle tip localization difficult in some patients. Magnetic resonance imaging also eliminates the risk of ionizing irradiation to radiologists and patients.

Conventional stainless steel biopsy needles, when used with MRI, produce imaging artifacts caused by an alteration in the homogeneity of the magnetic field. This magnetic force may also produce undesired movement of the needle. Magnetic resonance imaging-compatible needles incorporating alloys with increased nickel content that reduces imaging artifacts and almost completely eliminates the deflecting force of the magnets on the needle are now commercially available. Thus, MRI-guided fine-needle aspiration is a valuable diagnostic procedure because it permits the aspiration of head and neck lesions previously inaccessible by other means. Some investigators are now using the MRI-guided needle technique to attempt to deliver laser or radiofrequency energy as a possible treatment technique.

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Treatment of Laryngeal Dysphonias

IMPROVED UNDERSTANDING of the elements controlling the voice is leading to new surgical methods directed at different forms of dysphonia that have been difficult to manage. This heightened understanding has emerged through the efforts of researchers interested in laryngeal biomechanics, microscopic tissue elements, and neuromuscular control.

We now realize that the sound emanating from the vocal folds is produced by modulating airflow through a tissue wave. This traveling, or harmonic, wave is produced primarily by the loose connective tissue covering the fold, otherwise known as the lamina propria (cover). Physiologic alteration of the tissue wave, and ultimately the voice, occurs by contraction of the intrinsic and extrinsic laryngeal muscles (body). Thus, mass lesions that interfere with tissue wave propagation must be removed with as little disturbance of the loose connective tissue as possible. The use of lasers is seldom required; rather, microsurgery leaves the vocal fold edge as straight and intact as

possible. Defects in the lamina propria, such as sulci, atrophy, or scarring, must be corrected to ameliorate abnormal wave motion. In this regard, collagen or fat injections and mucosal grafts are being used with increasing frequency and success.

Almost as important as the cover-body theory has been the knowledge that the left and right vocal folds vibrate in unison, with both normally opening and closing simultaneously and in harmony. To accomplish this, both vocal folds must be brought together during phonation and must show similar viscoelastic properties. Phonosurgeons have begun to correct biomechanical inequalities between the vocal folds by surgically simulating the muscular contraction of the various intrinsic muscles. This is often accomplished by surgically modifying the laryngeal cartilaginous framework. Moving a window in the thyroid cartilage medially approximates the folds and simulates thyroarytenoid muscular contraction. The arytenoid cartilage can be adducted to simulate lateral cricoarytenoid and interarytenoid muscular contraction. Expansion or retrodisplacement of the anterior thyroid cartilage can be used to lengthen or shorten the vocal folds, leading to an alteration in the most comfortable pitch production. These operations on the laryngeal skeletal framework can be used to correct a weak voice or one with unusually high or low frequency.

Along with advances in understanding the biomechanics underlying vibration, the literature concerning the innervation of the larynx has grown. These neurophysiologic studies have encouraged surgeons to devise therapies to modify lost or diminished control of neuromuscular laryngeal function. Selective reinnervation of nerve and nerve muscle pedicles of the laryngeal muscle groups is gaining recognition as an effective means of improving neuromuscular function.

The convergence of scientific knowledge concerning tissue rheology, biomechanics, and neuromuscular control will soon lead to better reconstructive techniques after trauma or tumor ablation. The ultimate goal will be the ability to construct a new larynx from autologous tissues, and laryngeal transplantation is an intermediate but reachable goal within the next four to six years.

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Management of the Internal Carotid Artery in Skull Base Operations

ONE OF THE MOST IMPORTANT ADVANCES in the current management of head and neck cancer is skull base surgery. Patients previously doomed by the extension of upper aerodigestive tract malignant tumors to or through the skull base now have a reasonable chance of cure. With the close cooperation of head and neck, neurologic, and reconstructive surgeons, tumors that extend beyond the traditional boundaries of each discipline can now be successfully ablated by a team approach. The most successful efforts take place in institutions with designated, well-coordinated skull base surgery teams.

Tumor ablation is impeded when tumors encroach on or invade the middle cranial fossa and involve the internal carotid artery. The preoperative assessment of carotid artery involvement is difficult, but attempts to establish invasion of the vessel have been made using computed tomography and magnetic resonance imaging. The absence of a flow void or 360 degrees of arterial encirclement by tumor definitively establishes arterial invasion and mandates resection if cure is to be achieved. The lack of interface between tumor and vessel, as seen by these two methods or by ultrasonography, suggests no invasion. Displacement of the carotid artery, erosion of the petrous bone adjacent to it, or involvement of the cavernous sinus does not necessarily indicate vessel invasion.

Before surgical intervention, it is essential to study the relative safety of sacrificing the carotid artery. Is the collateral arterial supply sufficient to oxygenate the brain and prevent stroke if the carotid artery is taken? The most commonly used test to make this judgment is the internal carotid balloon occlusion test. With this test, the Seldinger technique is used to pass an intra-arterial balloon through the groin, placing it high in the cervical segment of the internal carotid artery. If the patient can withstand a 15- to 20-minute period of occlusion without having neurologic symptoms, then in 85% of cases, no ischemic stroke will develop if the carotid artery is taken. A number of techniques have been used to refine this test, such as radioactive and stable xenon testing before and after balloon test occlusion and the concomitant use of single-photon emission computed tomographic scanning and positron emission tomography. Transcranial Doppler testing and induced hypotension improve the predictive quality of the test. Unfortunately, no test is 100% reliable, and none can anticipate an embolic complication.

Although the preoperative assessment may indicate the possibility of internal carotid artery invasion by tumor, this scenario can only be established during the operation. If the tumor simply involves the periosteal lining of the carotid canal in the petrous bone, then this layer can be removed and the artery saved. Even if the adventitia of the vessel is involved, the artery can still be spared in benign tumors and most low-grade malignant tumors. Occasionally even a high-grade tumor can be successfully removed by peeling the adventitia off the artery. In most high-grade tumors, however, the artery must be taken.

In those cases where the balloon occlusion test is positive, a number of options exist. A patient could be informed that the procedure is too risky and that some palliative regimen such as irradiation or chemotherapy should be chosen. A staged procedure in which the superficial temporal artery is anastomosed to the middle cerebral artery can be done to reroute the circulation at a time before the definitive resection. The most common proce-

dure is a direct graft done at the time of resection. A saphenous vein graft replaces the resected artery usually from the high cervical segment to the petrous or cavernous portion. This operation has hazards and complications, such as strokes, meningitis, cranial nerve deficits, and death. It is essential to cover the graft with fresh vascularized tissue, preferably a free flap, and to isolate it from the upper aerodigestive tract.

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Olfactory Impairment

IMPAIRED OLFACTION (loss of sense of smell) is a common problem that deserves greater attention from clinicians and researchers. The most current estimate is that 2 million Americans suffer from an impaired sense of smell, but the actual number exceeds that estimate. An impaired sense of smell not only adversely affects culinary pleasures but also is a health hazard, for patients with an impaired sense of smell cannot smell smoke, gas leaks, or spoiled and rotten food. Odors are also an important part of our sensory environment, and patients with impaired olfaction lack the enjoyment of the environment and their loved ones and are handicapped in such simple matters as body hygiene. Although current research focuses on the gene coding for specific smell recognition and the ways in which we sense and process olfactory information, there is an ever-increasing awareness and understanding of the causes of impaired sense of smell. In an effort to assist primary care professionals in diagnosing and managing this disorder, the following information regarding its causes is offered.

Inflammatory rhinitis, be it allergic, infectious, irritative, or mixed, will impair the sense of smell when the inflammatory process involves the olfactory cleft, the roof of the nasal cavity wherein the olfactory epithelium resides. This is best diagnosed with coronal computed tomographic scans. Conductive defects, those conditions in which air and odorants do not reach the olfactory epithelium, seem to occur only when the nose is totally occluded or the olfactory cleft totally obstructed. Septal deflection is not a cause of an impaired sense of smell. Bilateral choanal atresia and large nasal tumors, such as severe nasal polyposis or a large meningomyelocele, are occasionally causes.

Olfactory impairment is common during upper respiratory tract viral infections. In some viral infections occurring during the middle and late years of life, the olfactory epithelium appears to be destroyed, causing an irreversible hyposmia. In such cases, inflammatory disorders, such as ethmoiditis, must be excluded.

Head trauma, typically from a frontal or occipital blow, can stretch or shear the olfactory nerves. If stretched, the sense of smell often returns. If sheared, olfaction rarely, if ever, recovers. Neurosurgical approaches to the floor of the anterior cranial fossa often necessitate cutting the olfactory fila; the resulting olfactory impairment is complete and permanent.

Exposures to various toxic chemicals and pollutants can cause olfactory impairment. Exposures severe enough to cause mucosal injury and burning can impair the sense of smell with a single exposure. Long-term exposure to certain known toxic chemicals, such as formaldehyde, ammonia, acetone, and many other noxious chemicals, may also destroy olfaction.

Congenital causes are recognized. Some are due to genetic deficiencies; others to probable neonatal or early childhood trauma. Certain genetic metabolic diseases are associated with an impaired sense of smell, Kallmann's syndrome (hypogonadotropic eunuchoidism) being the best known.

A recently recognized cause includes neurologic degenerative disease. Impaired olfaction has now been clearly documented to occur with Alzheimer's disease, Parkinson's disease, and Huntington's chorea. Aging itself is a well-known cause of olfactory impairment. It has been estimated that virtually everyone reaching their sixth or seventh decade has some smell impairment, and for many it is such that they feel they can smell and therefore "taste" nothing. As many as 50% of octogenarians are known to be anosmic.

Persons who have had a laryngectomy often have nasal congestion and a lack of nasal air flow and are effectively anosmic. Certain endocrine abnormalities, such as Addison's disease, Cushing's syndrome, hypothyroidism, diabetes mellitus, and numerous pituitary abnormalities, are associated with an impaired sense of smell. Although it is reported that certain nutritional deficiencies, such as of vitamins A, B_6, B_{12}, and trace-metal deficiencies, such as zinc and copper, impair the sense of smell, these are uncommon causes.

A field of increasing interest is the effect of drugs on olfaction. Several medications, such as corticosteroids, anticancer agents, antirheumatics, antithyroid hormones, hypolipidemic medications, psychopharmaceuticals, sympathomimetics, and others, can cause olfactory disturbances. These are diagnoses of exclusion. Drug-induced impairments typically occur with long-term exposure; hence, it is difficult to correlate the use of such medications with the impaired sense of smell. Several medical or surgical interventions have been associated with smell impairment. Any intranasal procedure can destroy the olfactory receptors. Radiation therapy, arteriography, influenza vaccination, and surgical therapy on the adrenocortical axis are all recognized causes.

Impaired olfaction is a common and increasing problem. To those who are impaired, it can be anything from a nuisance to a major disability. Physicians should be sensitive to the complaints of smell-impaired patients and, when appropriate, ensure proper referral and evaluation.

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Positron Emission Tomographic Imaging of the Head and Neck

ALTHOUGH POSITRON EMISSION TOMOGRAPHY (PET) has been used primarily as a research tool, advances in this technology have made it a powerful diagnostic tool as well. It complements the information obtained from computed tomography (CT) and magnetic resonance imaging (MRI) by demonstrating disorders of function in the absence of any anatomic abnormalities. Positron emission tomography produces images that reflect the distribution of decaying radioisotopes in vivo. Some radioactive isotopes decay by emitting a positron (positively charged electron) that collides with a local electron, resulting in annihilation. This reaction releases two photons traveling at 180 degrees of each other that are then detected by opposite radiation detectors arranged in a ring around the patient. These short-lived radioisotopes are incorporated into compounds such as water, carbon dioxide, glucose, and receptor-binding ligands. Fluorine 18-labeled 1-fluoro-2-deoxyglucose (fludeoxyglucose [^{18}FDG]), for example, is a glucose analogue that can be used to measure local glucose metabolism.

Positron emission tomography is being investigated for use in head and neck tumors. In both primary and metastatic tumors, aerobic glycolysis is often increased. Using the glucose analogue ^{18}FDG, PET can delineate these areas of hypermetabolism and identify primary tumors not detected by anatomic imaging. For example, PET can detect head and neck lymphoma and squamous cell carcinoma, which are seen as areas of increased ^{18}FDG accumulation. Because some submucosal or superficial head and neck tumors do not distort tissue planes or invade adjacent structures, MRI and CT may not detect them. Similarly, postirradiation or postsurgical anatomic changes may appear similar to recurrent tumor by conventional techniques. Furthermore, small tumor-infiltrated lymph nodes that are judged nonmetastatic by MRI or CT sometimes are visible on PET because of their increased metabolic activity. Although increased ^{18}FDG uptake in lymph nodes is not pathognomonic for metastasis, early experience suggests that in some cases it may be a sensitive indicator of nodal disease. Overall, there is potential for improving the evaluation of malignant lesions.

Positron emission tomography is also under study to determine the effectiveness of radiation therapy in head and neck cancers. Patients undergoing chemotherapy or radiation therapy may be better managed now that PET can provide information on tumor regression. Tumors responding to therapy show decreased ^{18}FDG uptake, whereas sites of recurrence can be detected by increased uptake. Also, studies have shown that substantial correlation exists between ^{18}FDG uptake and histologic grade; this deserves further investigation.

Although PET is expensive and requires a nearby cyclotron for the synthesis of short-lived radioisotopes, it has the potential to detect carcinomas not evident with other imaging techniques such as MRI or CT. Rather than replacing MRI or CT, PET may complement these techniques in the management of head and neck cancers.

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Preserving Hearing in Acoustic Neuroma Removal

RECENT ADVANCES IN MICROSURGERY for the excision of acoustic neuromas now allow the hearing to be preserved. These tumors arise from the vestibular nerve; the facial and cochlear nerves are intimately adherent and at risk for injury during tumor removal. A team approach with a skilled microneurosurgeon and a neuro-otologist experienced in temporal bone operations is essential. Technical advances during the past decade in neuroimaging, audiology, neurophysiology, neuroanesthesia, and operating rooms with microsurgical instruments and continuous intraoperative monitoring make these procedures possible.

Magnetic resonance imaging (MRI) using radioactive gadolinium provides excellent multiplanar views of acoustic neuromas with detailed relationship to critical neural structures. Computed tomography (CT) complements the anatomic detail of MRI by showing the bony labyrinthine structures and internal auditory canal in the temporal bone. Details of temporal bone structure are important to preserve the semicircular canals and labyrinth while the internal auditory canal is opened with a high-speed drill to view the tumor.

Preoperative neuroimaging, audiometric and electrophysiologic evaluation with pure-tone testing, speech reception threshold, speech discrimination scores, and brain-stem auditory evoked responses are key prognostic indicators for preserving the hearing. A speech reception threshold of less than 50 dB and speech discrimination scores of greater than 50% are considered minimal "serviceable" hearing indicators for surgically preserving the hearing; yet simply "hearing spoken words" is a good practical assessment of "useful" hearing. These preoperative evaluations give surgeons invaluable information for surgical planning and for counseling patients regarding hearing preservation.

Selecting the operative approach often depends on the size and location of the tumor and the surgeon's preference. The suboccipital approach is preferred for larger tumors (1.0 cm in diameter) that extend into the posterior fossa, and the middle fossal approach is preferred for smaller tumors (<1.0 cm in diameter) within the internal auditory canal. The results of hearing preservation for each approach are similar with experienced surgeons.

The overall rate of hearing preservation with acoustic neuroma removal in the current literature ranges from 12% to 59%. With smaller acoustic neuromas (<1.0 cm), there is a greater chance of preserving the hearing (48% to 75% in recent series). Tumors of 1.0 to 2.0 cm have hearing preservation rates approaching 50%, but larger tumors (>2.0 cm) have a much poorer prognosis (0% to 20% hearing preservation) depending on preoperative hearing function. These results contrast with those formerly obtained with surgical acoustic tumor removal, which usually included deafness, facial paralysis, and a 10% mortality rate.

Success in preserving hearing with acoustic neuroma removal has grown steadily in the past decade. This is achieved in more than 50% of patients with smaller tumors, yet the results are less impressive in patients with large tumors. Advances in microsurgical techniques, intraoperative monitoring, and preoperative patient selection will continue to improve these results.

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Microvascular Free Flaps in Head and Neck Reconstruction

MICROVASCULAR FREE FLAPS have expanded the scope of options available for the reconstruction of head and neck defects that result from tumor ablation or trauma. The technique involves transferring soft tissue or bone with its vascular pedicle from a distant site to the head and neck region and reestablishing blood flow through the transferred flap by anastomosis of the vascular pedicle to vessels in the neck. In the past, major defects in the head and neck region were reconstructed using pedicled flaps. The length of the pedicle is a limiting factor with this reconstruction technique, and only a few flaps are available—generally muscle and skin flaps from the chest and back. With microvascular techniques, tissue can be transferred from distant sites.

Microvascular free flaps can be fasciocutaneous (skin with underlying subcutaneous tissue), myogenous, myocutaneous, osseous, osteocutaneous, osteomyocutaneous, or visceral. The common donor sites for fasciocutaneous flaps are forearm, lateral upper arm, scapular region, and lateral thigh. The most commonly used myogenous or myocutaneous free flaps are rectus abdominis and latissimus dorsi. These fasciocutaneous and muscle flaps are used to reconstruct soft tissue defects in the head and neck region. Important applications of these flaps have been in the reconstruction of massive defects involving the face, scalp, or cranium. Such defects are extremely difficult, if not impossible, to reconstruct with local and regional pedicled flaps because of the limited arc of rotation and surface area. These factors are eliminated with the use of microvascular free flaps. Furthermore, in the reconstruction of extensive craniofacial defects, a healthy vascularized free flap can effectively and reliably seal off the cranium from extracranial communication, minimizing the incidence of cerebrospinal fluid leak and intracranial infections.

A newer application of revascularized soft tissue flaps is the restoration of sensation to the area of the oral cavity and pharynx that has been resected. In such a case, the fasciocutaneous flap is harvested together with its sensory nerve, which is then anastomosed to an appropriate sensory nerve supplying the area of the defect being reconstructed, such as the tongue, floor of the mouth, or the pharynx. The purpose of reconstructing with such a "sensate" flap is to help restore the ability to swallow. The preliminary results appear encouraging, though large series are necessary to determine the efficacy of this technique. Various vascularized bone flaps can be harvested together with an overlying flap of skin for reconstructing mandibular or maxillary defects. The most important application of osseocutaneous free flaps is the reconstruction of the anterior mandibular arch. Common donor sites are the iliac crest, the fibula, and the scapula. Visceral flaps are also used in head and neck reconstruction, where a segment of the jejunum is used to reconstitute segmental pharyngeal and upper esophageal defects.

Free revascularized tissue transfer has many advantages over traditional pedicled flaps. As a variety of donor flaps from distant sites are available, a defect in the head and neck region can be "custom fitted" with a flap of appropriate size and contour in a single-stage procedure to restore form and function while not sacrificing these same needs at the donor site. Closing a defect and restoring function are possible with a single-stage procedure. After tumor ablation, reconstruction with vascularized tissue allows the patient to undergo postoperative radiation therapy with little risk of wound complications. This is particularly the case with defects involving the anterior mandible and oral cavity. Before the popularity of vascularized osseous flaps, this type of defect was often reconstructed with a stainless steel or titanium mandibular reconstruction plate and a pectoralis myocutaneous pedicled flap to cover the plate inside the mouth. This frequently resulted in intraoral plate exposure caused by the gravitational pull of the pedicled flap. Furthermore, the plate often eroded through the external skin during or after the completion of radiation therapy. The use of revascularized osseocutaneous flaps has virtually eliminated

these problems. The overall success rate for microvascular free flap reconstruction now approaches 95% when done by skilled, well-trained microvascular surgeons.

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Spasmodic Dysphonia and Laryngeal Botulinum Toxin Injection

SPASMODIC DYSPHONIA is a voice disorder characterized by intermittent, involuntary tightening or constriction of the larynx during phonation. The interruption of air flow results in staccato, jerking, labored speech (adductor spasmodic dysphonia). Occasionally vocal spasms can abduct or separate the vocal folds, resulting in breathy voice breaks (abductor spasmodic dysphonia). The severe impairment in communication that results from this unusual condition often causes patients to lose or change their jobs. In the past, patients were frequently thought to have underlying emotional conflicts or psychopathology for which the voice problem was a manifestation. Psychological and speech therapy generally yielded poor results and left patients frustrated. Surgical therapy with unilateral recurrent laryngeal nerve section yielded initially good results. It also "legitimized" spasmodic dysphonia as a treatable condition. In long-term follow-up, however, spasmodic dysphonia symptoms recurred following surgical therapy in many patients.

Over the past ten years, the integration of research efforts from many contributors has provided a new framework for understanding the underlying causes of this problem. "Spasmodic dysphonia" is now thought to be a focal laryngeal manifestation of dystonia, a neurologic condition analogous to the focal dystonias of writer's cramp, blepharospasm, and torticollis. As with other dystonias, a patient with laryngeal dystonia may have other affected areas (such as in Meige's syndrome or orofacial dystonia) and may have a family history of dystonia.

The treatment of spasmodic dysphonia has evolved from a scattered variety of psychological, behavioral, medical, and surgical therapies to direct first-line myoneural blockade with botulinum toxin. Botulinum toxin was first developed in the 1970s and 1980s as an alternative agent for the treatment of blepharospasm and strabismus. At a recent consensus conference of the National Institutes of Health, botulinum toxin was deemed safe and effective in the treatment of adductor spasmodic dysphonia.

Botulinum toxin is typically administered intralaryngeally in an electromyography laboratory. Adductor spasmodic dysphonia treatment is given by placing a hollow needle electrode percutaneously through the cricothyroid membrane and into the thyroarytenoid muscle, using electromyography during phonation to locate the muscle, which functions as a laryngeal adductor. After localization, the toxin is administered through the needle electrode. When electromyography is not used, the toxin may also be administered percutaneously into the thyroarytenoid muscle through the thyroid cartilage or by a transoral route, visualizing the vocal folds indirectly with a fiberscope or mirror. The toxin may be given unilaterally or bilaterally. Depending on the dosages used, an initially breathy voice is followed in three to six months by improved phonation. For many patients, this means a return to employment. As nerve regenerates, symptoms return, and patients may again undergo treatment with botulinum toxin. The abductor variety is treated by administering the toxin to the posterior cricoarytenoid muscle; this technique carries a higher risk of airway difficulties developing, and the voice results to date have not been as promising.

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Endoscopic Sinus Surgery

THE FOUNDATIONS OF endoscopic sinus surgery, also known as functional endoscopic sinus surgery, are based on understanding the structure and function of the paranasal sinuses. The surgical rationale, approach, and techniques have evolved over the past two decades. Today this procedure has replaced the ablative paranasal sinus procedures such as Caldwell-Luc, nasal-antral windows, and external ethmoidectomy.

Of patients with chronic sinusitis, 90% or more have chronic nasal obstruction, postnasal drainage, and facial pain or headaches. In patients in whom antibiotics and appropriate treatment directed at allergic nasal reactions are not effective, nasal cytologic examination and sinus computed tomographic scans should be done. If appropriate therapy with antibiotics, environmental control, and nasal corticosteroids as indicated by the evaluation does not resolve the patients' chronic sinusitis, surgical intervention is indicated. The indications for an endoscopic sinus operation are, therefore, chronic sinusitis refractory to medical treatment. Whether a condition is refractory to medical treatment is a decision made by patients when they feel that they have tried medications and are simply fed up with the disease and the lack of improvement.

The subjective results of endoscopic sinus surgery are excellent. In a recent large series with 18- to 24-month follow-up, 85% to 90% of patients had good to excellent symptomatic relief. Some patients with recurrent sinusitis may need antibiotic therapy but tend to respond quickly.

Some patients have required surgical revision because of scarring in the middle meatus; this also usually leads to successful control of the condition.

In theory, the resolution of chronic sinusitis after endoscopic sinus surgery is the result of better aeration and improved mucociliary transport through the ostiomeatal complex. Thus, an objective measure of operative results is often reported as patency rates of the ostiomeatal complex and of the maxillary sinus ostia in particular. In the past, nasal-antral windows through the inferior meatus have been used to improve the aeration of the maxillary sinuses. The windows have a high closure rate, 25% to 45%, at two-year follow-up. The patency rates with endoscopic sinus surgery are substantially better, about 90% three years after the operation.

The complication rate of this operation is low. One series of 6,000 patients reported 3 cases of cerebrospinal fluid leak and 2 of intraorbital bleeding; there were no fatalities and no loss of vision. The most frequent minor complications included epistaxis, epiphora, and transient diplopia. In a study of the most common complications, problems were diplopia caused by damage to extrinsic ocular muscles or nerves, blindness caused by retrobulbar hemorrhage or optic nerve injury, and intracranial complications, such as cerebrospinal fluid leak, meningitis, and hemorrhage. Though serious complications occur, it should be emphasized that when done by well-trained surgeons, the endoscopic sinus operation is a safe procedure.

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Alerts, Notices, and Case Reports

Rat-Bite Leptospirosis

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LEPTOSPIROSIS, considered the most widespread zoonosis in the world, is transmitted primarily through the direct or indirect exposure of mucous membranes or abraded skin to the urine of an infected animal. Although reported case rates are low in the United States, the protean manifestations and lack of active surveillance frequently lead to missed diagnoses.[1] Leptospirosis has traditionally been classified as an occupational illness of men, with recent trends showing an increasing proportion of exposures through avocational or recreational activities.[2] The ensuing report describes an unusual mode of transmission for leptospirosis, following a rat bite in the home.

Report of a Case

The patient, an 11-year-old Filipino girl, presented to the emergency department of a local hospital because of anorexia, emesis, and myalgias, primarily involving the lower extremities, for four days and fever, severe headache, and neck pain for one day. She had been seen ten days earlier in an outpatient clinic for a rat bite on her left second toe. The treatment included wound dressing with antibiotic ointment and the administration of a tetanus-diphtheria booster. The patient was noted to be residing with her family in an urban low socioeconomic area of Honolulu, Hawaii, in housing with known rat infestation. This was the first episode of a rat bite in the home.

On physical examination in the emergency department, she was thin, alert, oriented, and in mild distress due to neck and head pain. Relevant findings included a temperature of 40.4°C, a pulse rate of 90 beats per minute, a blood pressure of 103/57 mm of mercury, and respirations of 24 per minute. Her neck had a full range of motion although there was subjective pain with motion. Examination of the patient's left second toe revealed a superficial laceration proximal to the nail bed without erythema, edema, or drainage.

Laboratory studies elicited the following values: a peripheral leukocyte count of 5.4×10^9 per liter (0.69 segmented forms, 0.13 band forms, 0.10 lymphocytes, 0.07 monocytes, 0.01 eosinophils), a hematocrit of 0.38 (38%), and a platelet count noted to be adequate. Serum electrolyte analysis was remarkable only for mild hyponatremia (sodium level 128 mmol per liter). A urinalysis revealed a pH of 7 and a specific gravity of 1.018. There was no evidence of proteinuria or bilirubinuria, and microscopic examination showed no abnormalities. A lumbar puncture was done and revealed clear, colorless cerebrospinal fluid (CSF); analysis included a leukocyte count of 12×10^6 per liter (12 per μl) with 0.15 neutrophils, 0.62 lymphocytes, and 0.23 monocytes, and an erythrocyte count of less than 1×10^6 per liter (<1 per μl). The CSF glucose level was 4.2 mmol per liter (75 mg per dl), and the protein level was 0.24 grams per liter (24 mg per dl). Gram's stain examination of both CSF and urine specimens was negative.

The patient was admitted with the presumptive diagnoses of rat-bite fever and aseptic meningitis. The diagnostic evaluation included cultures of blood, urine, and CSF; rapid plasma reagin test; and serologic evaluation for leptospirosis. She was managed with the administration of intravenous penicillin G, 1 million units every four hours, intravenous fluids, and symptomatic treatment of pain and nausea. Her fever subsided, and her neck stiffness abated on the second hospital day. By the third hospital day, her headache had resolved and the patient was asymptomatic. The patient was discharged on the fourth hospital day. Her discharge medications included potassium penicillin V, 2 grams per day by mouth for ten days.

Cultures of blood and CSF specimens obtained on admission showed no growth. Urine culture was positive for *Lactobacillus* species, most likely reflecting vaginal contamination. The rapid plasma reagin test was nonreactive. A serum specimen drawn on hospital day 2 and a specimen drawn three weeks later were tested for antibodies to leptospires at the Centers for Disease Control and Prevention reference laboratory using the microscopic agglutination test. Whereas the specimen drawn during the acute phase was negative, the one taken during the convalescent phase was positive for *Leptospira interrogans*, serovar *mankarso* (serogroup *icterohaemorrhagiae*), with a titer of 1:3,200, confirming the diagnosis of leptospirosis. As part of the case investigation, Hawaii State Department of Health personnel set up rat traps in the home. Of 11 rats (*Rattus norvegicus*) trapped, 3 had kidney cultures positive for *Leptospira* of the same serogroup as found in the case-patient.

Discussion

Leptospirosis is transmitted to humans primarily by direct or indirect contact with the urine of infected animals. Leptospires may enter the body through intact mucous membranes or abraded skin.[3] The domestic rat (*R norvegicus*) may serve as the primary reservoir of leptospirosis in urban areas. At least 78% of rats trapped in

(Gollop JH, Katz AR, Rudoy RC, Sasaki DM: Rat-bite leptospirosis. West J Med 1993; 159:76-77)

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urban inner-city Detroit, Michigan, showed serologic evidence of leptospirosis.[4] The six-day time period between the rat bite and the onset of illness corresponds to the usual incubation period for leptospirosis—3 to 10 days.[3] Although transmission associated with animal bites is unusual, cases have been reported with bites from rats,[5-7] a dog,[8] a mouse,[9] and after mouth-to-mouth resuscitation with pigs.[10] Although saliva is not considered an infectious fluid, that from animals in the acute phase of the disease may contain leptospires.[11] Animal-bite–associated transmission has been attributed to either direct inoculation from urine contamination in an animal's mouth or the skin wound serving as a portal of entry for leptospires in the immediate environment.[3]

From 1980 through 1990, the total number of cases reported each year in the United States ranged from only 40 to 100.[12] Surveys of inner-city populations, however, have demonstrated substantial leptospiral seroprevalence rates: 31% of urban youths in Detroit[13] and 16% of inner-city adults in Baltimore, Maryland.[14] Active case finding during a 54-month period in urban St Louis, Missouri, uncovered 9 confirmed and 25 presumptive cases in children.[15] Active surveillance in Hawaii led to a greater than fivefold increase in reported rates.[16]

Subclinical infections are common, and most clinical infections are self-limiting.[3] The most frequently reported symptoms associated with clinical illness are nonspecific and include fever, headache, and myalgias.[1,3] Leptospirosis is most commonly misdiagnosed as aseptic meningitis, fever of unknown origin, or a viral syndrome.[2] The diagnosis may be confirmed by culturing of the organism from blood, CSF, or urine or by demonstrating serologic evidence of infection. The isolation of leptospires from body fluids requires special laboratory techniques, media, and a prolonged incubation time (as long as 6 weeks); hence, serologic testing is the usual means of laboratory confirmation.[3] The Leptospirosis Reference Laboratory of the Centers for Disease Control and Prevention in Atlanta, Georgia, provides serologic diagnostic services and serotyping of positive leptospiral cultures. Physicians desiring this service should contact their respective state health department laboratory or communicable disease unit for advice and assistance in submitting specimens.

Recently conducted double-blind, placebo-controlled trials evaluating the efficacy of antibiotics in the treatment of leptospirosis have shown oral doxycycline, 100 mg twice a day for seven days, to be effective in modifying the disease course in patients with anicteric illness when treatment is initiated within four days of clinical onset.[17] Parenteral penicillin G, 6 million units daily for seven days, showed efficacy in modifying illness in patients with severe icteric disease even when therapy was initiated 7 to 19 days after the symptoms began.[18] Because laboratory confirmation of leptospirosis may take weeks, therapeutic intervention should be instituted as soon as the diagnosis is suspected.

Empiric antibiotic treatment should be considered for any patient presenting with a febrile illness for which there is a history of direct contact with animals or contaminated water or soil within 2 to 26 days of the start of symptoms, especially when symptoms had an abrupt onset and consist of severe headache, chills, myalgias primarily affecting the lower extremities, nausea, and vomiting.[3,19-22] Although conjunctival suffusion has been noted as a pathognomonic feature, it is frequently absent, whereas jaundice occurs in less than 40% of reported cases.[2] For severe cases, parenteral penicillin is considered the drug of choice; less severe cases may be treated with oral tetracycline or doxycycline.[3,20-23] Uncontrolled studies have also reported therapeutic efficacy with ampicillin and amoxicillin.[24]

Because rat infestation is a well-recognized, inner-city housing problem, it is clear that leptospirosis cases from these areas are going unrecognized and hence underreported. Leptospirosis should be included in the differential diagnosis of all patients with rat exposure (including bites) presenting with a febrile illness, as early diagnosis and treatment have been effective in modifying the course of the illness.

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Eosinophilic Meningitis Due to *Angiostrongylus cantonensis*

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VARIOUS HELMINTHIC INFECTIONS may cause eosinophilic meningitis, of which the most common in Australia and the South Pacific is the rat lungworm, *Angiostrongylus cantonensis*.[1] The diagnosis is usually suggested by clinical and epidemiologic features and confirmed with positive serologic tests.

The disease is an immediate complication of vegetarianism because humans usually become parasitized when they ingest vegetables contaminated by rat feces.

We describe four cases of this disease. All four patients are vegetarians. In the first patient, the disease was particularly severe, presumably reflecting a high parasite load. The other cases occurred in one family and illustrate how the severity of symptoms usually correlates with exposure to contaminated food.

Report of Cases

Patient 1

The patient, a 25-year-old male vegetarian who resided in Byron Bay, New South Wales, Australia, was seen because for two weeks he had had progressive lower limb weakness, dysesthesia of the feet, urinary incontinence, confusion, and visual hallucinations. Because of rapidly increasing weakness, he was transferred to the Royal Melbourne Hospital, Prahran, Victoria, Australia, in the fourth week of his illness. Before admission he had been living in an abandoned house infested with rats. His diet comprised home-grown vegetables that were rarely washed. He admitted to illicit drug use, including amphetamines, cocaine, and golden "magic" mushrooms.

On examination the patient was drowsy and disoriented and had a temperature of 37.5°C (99.5°F), moderate neck stiffness, and photophobia. Cranial nerves and fundi were normal. Motor power was globally decreased to 3/5 in all limbs, and areflexia and bilateral extensor plantar responses were noted. Sensation to pinprick was decreased below T-5. Anal tone was decreased, and an indwelling catheter was inserted for urinary retention.

(Fuller AJ, Munckhof W, Kiers L, Ebeling P, Richards MJ: Eosinophilic meningitis due to *Angiostrongylus cantonensis*. West J Med 1993; 159:78-80)

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Cerebrospinal fluid (CSF) examination revealed the following: erythrocytes, 2×10^6 per liter; lymphocytes, 245×10^6 per liter; eosinophils, 75×10^6 per liter (22% of total leukocyte count); and monocytes, 19×10^6 per liter; the protein level was 1.01 grams per liter and glucose 1.9 mmol per liter. The CSF pressure was elevated at 33 cm of water. He had a peripheral blood leukocyte count of 21.2×10^9 per liter, of which 6.1×10^9 per liter (29% of total leukocyte count) was eosinophils (normal, 0.04 to 0.44) (Table 1). His erythrocyte sedimentation rate was 93 mm per hour (normal, 0 to 11). Liver function test results and a chest x-ray film were normal. Nerve conduction study findings were consistent with a multilevel radiculopathy. Electroencephalography showed generalized slowing of the background activity, consistent with an encephalopathy. A myelogram and cerebral computed tomographic (CT) scan were normal. Magnetic resonance imaging revealed a mild increase in ventricular size but no intraparenchymal lesion. Serologic tests for Epstein-Barr virus, human immunodeficiency virus, hepatitis B surface antigen, and CSF cryptococcal antigen were negative, as were cultures for *Cryptococcus* species and *Mycobacterium tuberculosis*. Serologic tests for *A cantonensis* (at another hospital) were initially negative at week 5 and became strongly positive at week 8.

Five weeks after his illness began, the patient's condition deteriorated, with fevers as high as 39°C (102.2°F) and complete lower limb paralysis. A spontaneous pneumothorax developed that required an intercostal catheter and was complicated by a bronchopleural fistula. Liver function test values became progressively abnormal with an alkaline phosphatase of 344 U per liter (normal, 0 to 90); bilirubin, 5 μmol per liter (normal, 0 to 19); aspartate aminotransferase, 331 U per liter (normal, 0 to 43); alanine aminotransferase, 363 U per liter (normal, 0 to 55); and γ-glutamyltransferase, 415 U per liter (normal, 0 to 50). A hepatic ultrasonogram was normal. Treatment with intravenous hydrocortisone sodium succinate, 100 mg every six hours, was started empirically; four days later this was changed to oral prednisolone, 75 mg daily. His clinical state improved. His confusional state resolved by week 7 of the illness, and there was a gradual return of upper and lower limb power. Fecal continence was regained, but recurrent urinary retention necessitated self-catheterization. Painful peripheral dysesthesias became a major problem as sensation returned. The peripheral blood eosinophilia resolved after steroid therapy was started, and there was resolution of the bronchopleural fistula. The liver function test values had returned to normal by week 13, and the erythrocyte sedimentation rate returned to normal by week 16. Steroid therapy was discontinued at week 17. The patient was discharged home six months after the onset of the illness, requiring the use of two canes for ambulation.

Patient 2

The patient, a 33-year-old woman, was admitted to the Austin Hospital, Heidelberg, because for three weeks she had had midthoracic back pain. This was associated

ABBREVIATIONS USED IN TEXT

CSF = cerebrospinal fluid
CT = computed tomographic

with hyperesthesia initially involving the left arm, then spreading to involve the whole body from the midthoracic region down.

Two weeks later, frontal headaches, photophobia, fevers, and diplopia developed. The patient was an Australian who had been residing in Vanuatu (formerly New Hebrides) for the past ten years. She returned to Australia for further medical care. Ironically, she was married to the manager of the local abattoir, but had recently commenced a vegetarian diet. She purchased salad vegetables from the markets in Port Vila, Vanuatu, which were not washed before consumption. She did not eat shellfish.

On examination, she had a temperature of 37.4°C (99.3°F). She had pronounced cutaneous hyperesthesia, being unable to tolerate the feel of clothing or bedsheets on her skin. She had photophobia and mild neck stiffness. There was a partial left sixth cranial nerve palsy. The fundi were normal. Further findings of the examination were unremarkable.

A CT scan of the brain was normal. A lumbar puncture was done, and the CSF pressure was elevated at 44 cm of water. The CSF glucose content was 2.7 mmol per liter, and the protein value was 0.37 grams per liter. The cell count showed lymphocytes, 160×10^6 per liter; eosinophils, 48×10^6 per liter (22% of total leukocyte count); neutrophils, 12×10^6 per liter; and erythrocytes, 5×10^6 per liter. The CSF cryptococcal antigen test and cultures for *Cryptococcus* species and *M tuberculosis* were negative.

Her peripheral leukocyte count was 12.2×10^9 per liter with eosinophilia (18%). Serum electrolyte tests showed a lowered sodium level of 116 mmol per liter. Serum and urine osmolalities confirmed a diagnosis of inappropriate antidiuretic hormone secretion. Liver function test results, a chest x-ray film, and x-ray films of the thoracic spine were normal.

A clinical diagnosis of eosinophilic meningitis due to *A cantonensis* was made. She was treated with bed rest, analgesia, antiemetics, and carbamazepine for her severe prominent hyperesthesia. A mild bilateral papilledema and a partial left third nerve palsy developed that resolved subsequently. She required further lumbar punctures for the relief of headaches. She was discharged from hospital a month after admission and returned to Vanuatu, where she is currently well. Serologic tests on admission were positive for *A cantonensis*.

Patients 3 and 4

Patient 2 had two sons, aged 11 and 12, who were transferred to the Austin Hospital five days after their mother's admission. Both had partially embraced their mother's new diet. They had similar though milder symptoms and signs and recovered more quickly than their mother. The younger son, patient 3, had a CSF pressure of 23 cm of water with a glucose level of 2.5 mmol per liter and a protein value of 0.54 grams per liter. The CSF cell count was as follows: neutrophils, 80, lymphocytes, 440, and eosinophils, 200×10^6 per liter (28% of total CSF leukocyte count). The older son, patient 4, had a CSF pressure of 30 cm of water, with a CSF glucose level of 3.2 mmol per liter and protein content of 0.50 grams per liter. His CSF contained 180×10^6 per liter lymphocytes, 120×10^6 per liter eosinophils (40% of total), and 170×10^6 per liter erythrocytes.

An independent 8-year-old daughter who had not cooperated with the family's dietary change remained well. The patient's husband had mild symptoms but was reluctant to be investigated.

Discussion

Angiostrongylus cantonensis is a parasite found in Australia,[1] Hawaii,[2] Thailand,[3] Japan, China, Vietnam, Cambodia, Papua New Guinea, Indonesia, the Philippines, Taiwan, Vanuatu, and several smaller Pacific Islands.[2] In previously reported Australian cases, infection has been acquired only in the state of Queensland, and patient 1 represents the first reported case of *A cantonensis* infection acquired in the state of New South Wales.

Adults of the rat lungworm, *A cantonensis*, reside and lay their eggs in the pulmonary arteries of rats and other rodents.[2] After hatching, the larvae break into the alveoli, migrate up the respiratory tract, are swallowed, and pass out with the feces. They develop into second- and third-

TABLE 1.—*Clinical Features of Patients With* Angiostrongylus cantonensis *Eosinophilic Meningitis*

Patient	Sex	Age, yr	Clinical Features	CSF Opening Pressure, cm water	CSF Protein, grams/liter	CSF Glucose, mmol/liter	Leukocyte Count (Eosinophil)* CSF, $\times 10^6$/liter	Leukocyte Count (Eosinophil)* Blood, $\times 10^6$/liter
1	M	25	Meningoencephalitis; residual neurologic sequelae; possible pulmonary and hepatic involvement	33	1.01	1.9	339 (0.22)	21.2 (0.29)
2	F	33	Severe meningitis; hyperesthesia; cranial nerve palsy	44	0.37	2.7	220 (0.22)	12.2 (0.22)
3	M	11	Mild meningitis	23	0.54	2.5	720 (0.28)	10.0 (0.18)
4	M	12	Moderate meningitis; hyperesthesia	30	0.50	3.2	310 (0.39)	8.4 (0.34)

CSF = cerebrospinal fluid

*Given as a fraction of 1.00.

stage larvae within their natural intermediate hosts, such as slugs and snails, notably the *Pila* species commonly eaten in Thailand. Freshwater prawns, land crabs, and frogs have been found to harbor the third-stage larvae of the parasite as a result of eating infected intermediate hosts. Humans, like rodents, become parasitized when they ingest infected molluscs, contaminated vegetables, or fomites. Larvae migrate to the brain, where they grow and subsequently travel to the lungs to deposit eggs. In humans, the nematode does not complete its life cycle, usually dying after reaching the central nervous system.[3]

A cantonensis infections are usually mild, with headache, nausea, photophobia, and neck stiffness as the predominant symptoms.[2] Severe peripheral paresthesia may be a diagnostic clue. Generalized weakness, visual disturbances, and extraocular muscle palsies are also well described,[2,3] but urinary retention, ataxia, and spinal cord lesions in humans are rare. Fever exceeding 38°C is uncommon.[5] Hepatic and pulmonary involvement have not been previously reported. Although not proved in the first case, no other cause was found for the pneumothorax and bronchopleural fistula or for the abnormal values on liver function tests. Resolution of the abnormal liver function correlated with the clinical resolution of the illness and with the administration of steroids.

Most cases of angiostrongyliasis in humans are self-limited, and recovery without sequelae is the rule. A number of cases of greater severity and chronicity have been reported, however, and these may correlate with a higher parasite load.[1,6] In patients 2, 3, and 4, the severity of the illness was directly related to the amount of unwashed lettuce each patient consumed.

The diagnosis of *A cantonensis* meningitis is suggested by the triad of typical clinical presentation, a history of exposure through eating intermediate hosts (such as shellfish) or contaminated food (such as unwashed watercress or lettuce), with cerebrospinal fluid eosinophilia. Staining of CSF for eosinophilia must usually be specifically requested. Positive serologic testing using an enzyme-linked immunosorbent assay is confirmatory.[7]

The differential diagnosis of *A cantonensis* meningitis includes cerebral cysticercosis, the only other infection in the Pacific region documented to occasionally cause CSF eosinophilia in excess of 10%.[8] Cerebral involvement with this parasite is rare and will usually present with symptoms or signs of a space-occupying lesion. In Southeast Asia, particularly Thailand, an intense eosinophilic pleocytosis can also be caused by *Gnathostoma spinigerum*.[3] The presenting symptom is often sharp pain from irritation of a nerve root. Myeloencephalitis with limb paralysis is common, and severe disabling sequelae may occur. The CSF is often bloody or xanthochromic. A serologic test for *Angiostrongylus* species does not cross-react with that for *G spinigerum*. *G spinigerum* is not known to occur in Australia or the Pacific Islands.

There have been a few reports of CSF eosinophilia associated with *Toxocara canis*, *Trichinella spiralis*, *Ascaris lumbricoides*, *Echinococcus granulosus*, and *Strongyloides stercoralis* infections.[8] In these cases, CSF eosinophilia is usually less than 10% and may be purely a result of intense peripheral eosinophilia. Similarly, neurosyphilis, tuberculous meningitis, and lymphomas may uncommonly cause mild CSF eosinophilia, but not to the degree seen in our patients.[8]

The optimal regimen for treatment is not established. Anecdotal reports exist for the efficacy of thiabendazole[3,9] and diethylcarbamazine citrate,[10] but anthelmintic drugs have not been shown conclusively to be beneficial in humans. Corticosteroids may be helpful in alleviating symptoms of raised intracranial pressure and in reducing allergic reactions to living or dead larvae.[2]

The disease is largely prevented through the control of rats. The proper washing of vegetables and cooking of snails and aquatic crustaceans are also important.

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Accidental Poisoning by Warfarin-Contaminated Herbal Tea

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AMERICAN CITIZENS, especially those living near the United States-Mexico border, frequently shop in Mexico. We report the case of a patient presenting with a coagu-

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lation disorder apparently engendered by drinking warfarin-contaminated hibiscus tea purchased in Tijuana.

Report of a Case

The patient, a 41-year-old woman with a history of interstitial cystitis, was seen because of hematuria and left flank pain for two days. A urinalysis revealed yellow color, slight proteinuria (1+), and an erythrocyte count of more than 50 per high-power field. A urine specimen was submitted for culture, and a three-day course of the combination drug of trimethoprim and sulfamethoxazole was started. The patient was seen two days later with continued flank pain and no response to the antibiotic therapy. The urine culture showed no growth. An intravenous pyelogram done that day was normal. The patient was treated with analgesics, and on the following day she noted that the flank pain, though still present, was notably diminished. She also had a recent onset of mild headache, fatigue, and mild dyspnea on exertion, and over the past several months she had noticed easy bruising. A physical examination revealed no abnormalities other than several small ecchymoses distributed on the trunk and the lower extremities. A urinalysis showed rare leukocytes and erythrocytes on microscopic examination. On a complete blood count she had a hematocrit of 0.27 (27%) and a hemoglobin of 87 grams per liter (8.7 grams per dl) with normal indices. The leukocyte count and differential cell count were within normal limits. The platelet count was 534×10^9 per liter. The patient's prothrombin time was 30.0 seconds with a control of 12.3 seconds (international normalized ratio [INR] 11.5).* Her partial thromboplastin time was 36.8 seconds with a control of 27.9 seconds. The prothrombin time performed with a 1:1 mix corrected to 12.5 seconds with a control of 12.1 seconds (INR 1.1); the partial thromboplastin time with a 1:1 mix corrected to 28.1 seconds and a control of 27.2 seconds. Factor II and factor VII levels were 6% and 5% of normal, respectively.

The patient was admitted to the hospital with the diagnosis of coagulation disorder due to prothrombin-complex deficiency. An extensive history failed to disclose any possible sources of purposeful or accidental warfarin ingestion. Phytonadione, 10 mg, was administered subcutaneously daily and then iron sulfate, 325 mg, orally daily. Within 60 hours of admission, the patient's prothrombin time had dropped to 13.5 seconds with a control of 12.2 seconds (INR 1.3). Her symptoms resolved over the ensuing days, and her recovery was uneventful. A high-performance liquid chromatographic assay of her serum (Hewlett-Packard 1090 high-performance liquid chromatograph using UV detection at 280 nm, performed by Poisonlab, Inc, San Diego, California) returned positive for warfarin. At the time of discharge, extensive efforts by the patient and her physicians failed to elucidate a plausible source for warfarin ingestion. The patient was specifically asked about the possibility of a surreptitious administration of warfarin by herself or family members and denied any possibility of this.

During a follow-up visit five days after discharge, the patient told her family physician of her suspicions that one or more of several herbal teas that she had purchased in Tijuana might contain warfarin. The patient deduced this possibility because her husband and children were found to have normal prothrombin times, and this was the only substance ingested solely by her. Several samples of brewed tea were sent for warfarin assays. One hibiscus tea sample (Lagg's Jamaica Tea, manufactured in Mexico City) returned positive for metabolic products of racemic warfarin (same method and company). This was immediately reported to the San Diego County Department of Health Services, the Food and Drug Branch of the California Department of Health Services, the United States Food and Drug Administration, and the appropriate public health agencies in Mexico. In addition, the tea manufacturer was notified.

Discussion

The anticoagulant effect of bishydroxycoumarin was first reported in 1922 by Schofield, who described a hemorrhagic disease of cattle following feeding on spoiled sweet clover silage.[1] This came to be known as "sweet clover disease" and led to the discovery of the anticoagulant properties of coumarin. Warfarin induces its anticoagulant effect by inhibiting vitamin K epoxidereductase, which in turn diminishes production of the reduced form of vitamin K. The depletion of reduced vitamin K diminishes the γ-carboxylation of vitamin K-dependent coagulant proteins (prothrombin and factors VII, IX, and X) and the anticoagulant proteins C and S, which in turn decreases their biologic activity. Warfarin sodium is the most commonly used of the coumarin compounds in North America.[2] In addition to its use in human medicine, warfarin is a widely used rodenticide, readily available in many commercial preparations.

Warfarin has been used in attempted homicides,[3] ingested surreptitiously,[4] and administered surreptitiously by parents to children.[5,6] One of the saddest epidemics of warfarin poisoning occurred in Ho Chi Minh City (Saigon), Vietnam, in August 1981 when 177 infants died of exposure to warfarin that was transdermally absorbed through contaminated talcum powder.[7] This epidemic took place in several provinces in Vietnam and involved several different brands of talcum powder. The cause of the warfarin contamination was not discovered.

The point of contamination of the hibiscus tea in our study is not known precisely, but it is surmised to have taken place at or before the point of manufacture. Warfarin might conceivably be present in warehouses or agricultural settings. Moreover, the tea was purchased in a sealed box without evidence of tampering, and the tea came in sealed tea bags. This patient and her family's primary care physicians discount surreptitious ingestion as a plausible explanation.

To prevent the possibility of similar episodes, the patient and several of her primary care providers held a

*The international normalized ratio is a standardized method of reporting prothrombin times to ensure that a uniform intensity of oral anticoagulant therapy is used worldwide.

press conference to alert the populace to the possibility of warfarin intoxication from this product. In addition to widespread press coverage, several major television stations in San Diego reported this story. To our knowledge, there have been no other cases of warfarin intoxication from this product in San Diego.

Despite the large number of US travelers to Mexico, we think that the risk of this type of poisoning is relatively low. Nonetheless, we suggest that travelers be counseled that standards of food safety in third world countries may be considerably lower than in the United States.

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Special Series

Benefits of Stopping Smoking

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This article launches a special WESTERN JOURNAL OF MEDICINE *effort to help prevent disease and disability. Erica Frank, MD, MPH, an Assistant Professor in the Department of Community and Preventive Medicine and Department of Medicine, Emory University School of Medicine, and Adjunct Professor at the Emory University School of Public Health, Atlanta, Georgia, will head the endeavor. The goals are to present scientific foundations for prevention and to provide practical ways to improve patients' lives. This first article addresses smoking cessation. We may think that we know it all, but we may not, and patients do not: about 25% of Americans smoke, and more than half of persons who ever smoked began their fatal habit before they were 18 years old. Side-stream smoke affects adults and children adversely, too, causing inflammation, infection, and cancer. Smokers need to stop smoking, and young people need to not start. Dr Frank's review is accompanied by a page for patients. It debunks myths and is designed to be duplicated so patients can leave their physician's office with a new lease on life in hand. Look for future prevention-oriented articles in this series that feature science and patient education.*

LINDA HAWES CLEVER, MD
Editor

Although physicians can easily list illnesses attributable to smoking, it may be more difficult to describe specific benefits of stopping smoking. I will summarize the known health benefits that follow the cessation of smoking. The companion patient information sheet should help stimulate discussions with patients about issues related to smoking cessation.

Highlights

- For those who quit smoking at age 35, it is estimated that women add about 3 years to their life expectancy and that men add more than 2 years.
- Smokers are at least twice—and as much as 6 times—as likely to have a myocardial infarction as are nonsmokers; those who stop smoking for 2 years have about twice the risk of having a myocardial infarction as never-smokers; and, after stopping for more than 2 to 4 years, their risk is not significantly different from that of those who have never smoked.
- About 53,000 persons die each year in the United States of the effects of the passive inhalation of tobacco smoke. This estimate includes about 37,000 deaths from heart disease and 3,800 deaths from lung cancer.
- Although 79% of smokers gain weight after quitting smoking, they gain an average of only 2.3 kg (5 lb).

The benefits of stopping smoking are substantial and compelling. The 1990 Surgeon General's report reasserted that smoking cessation is both desirable and achievable.[1] Although cigarettes are responsible for one of every six deaths in the United States (approximately 1,000 deaths per day), it is encouraging that more than 38 million Americans have voluntarily quit smoking.

Morbidity and Mortality

A number of large studies have documented reductions in overall mortality following smoking cessation. The Coronary Heart Disease Policy Model projected that 35-year-old men would live 2.3 years longer if they quit smoking and that 35-year-old women would gain 2.8 years.[2] Mattson and colleagues found that a smoking-related disease will kill 16% of heavy smokers by age 65, 28% by age 74, and 36% by age 84.[3] The Coronary Artery Surgery Study found that in 1,893 men and women aged 55 years and older, the relative risk of death for smokers versus that for former smokers was 1.7[4]; the US Veterans Affairs study (n = 293,958 men) found a relative risk of 1.4[5]; and Friedman and colleagues reported, after adjusting for baseline differences, a relative mortality risk of 1.6 in 25,917 men and women.[6]

For both men and women, the relative risk of death for smokers versus that for never-smokers ranges between 1.5 and 2.5, with men at higher risk than women and a dose-response by number of cigarettes per day. The risk declines to 1.5 to 2.0 times that for never-smokers by 5 years of abstinence from cigarettes and, in many studies, to equivalence with never-smokers after 15 years, particularly for those who smoked less than a pack per day.[1]

The dose response of smoking across disease processes is both marked and consistent, at least in men. Those who smoke fewer cigarettes a day have lower relative risks of death from all causes, all cardiovascular diseases, coronary heart disease, stroke, influenza and pneumonia, aortic aneurysm, all respiratory diseases,

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bronchitis and emphysema, all cancers, and lung cancer than do those who smoke more.[1,5]

Risk tends to diminish in relation to years of cigarette abstinence, best shown for all-cause mortality and total cardiovascular disease-related mortality.[5] Smoking cessation's effect on overall morbidity is more difficult to document, as indices of health vary among studies, and most studies fail to identify those smokers who quit because of ill health.[1]

Pulmonary Disease

Improvements in the rates of both malignant and nonmalignant pulmonary diseases and in risks for those diseases are substantial with smoking cessation. Cigarette smoking is the major cause of chronic obstructive pulmonary disease in Americans, accounting for approximately 84% of deaths among men and 79% among women due to this disease.

Former smokers are less likely than are current smokers to have chronic coughs. Six studies cited in the Surgeon General's report found in men a range for prevalence of cough of at least three months per year of 13% to 41% for current smokers, 2.9% to 13.0% for ex-smokers, and 0.0% to 11.0% for never-smokers. Three studies in the same report found a range for women of 9.1% to 31.8% for current smokers, 7.5% to 10.0% for ex-smokers, and 4.0% to 5.6% for never-smokers.[1] A prospective study found a decrease in the prevalence of chronic cough from 11.2% to 1.8% in 623 white men who had smoked at least a pack per day and then had quit.[7]

Ex-smokers have less phlegm production and wheezing, higher forced expiratory volume in one second and vital capacity, less small airway disease and bronchial reactivity, better immune function, and lower mortality from influenza and pneumonia, pulmonary tuberculosis, bronchitis and emphysema, or asthma than do current smokers.[1,5,8] Although some pulmonary damage is irreversible, many pulmonary risks begin to decrease within a few weeks to months of abstinence from smoking.[1]

Smoking cessation clearly decreases the risk of lung cancer. The disadvantages of continued smoking begin at a cellular level, before the onset of disease. Smokers are more likely to have atypical cells in their bronchial epithelia than are ex-smokers or never-smokers—93.2% of smokers, 6.0% of ex-smokers, and 1.2% of never-smokers have such cells—and are more likely to have DNA damage.[1] Smokers are more likely than are ex-smokers or never-smokers to have pulmonary epithelial, possibly precancerous, lesions.[9] Continued smoking may adversely affect the prognosis for lung cancer. In a study of 112 patients treated for small-cell lung cancer, those who had stopped smoking before their diagnosis had the best survival rates, those who stopped at the time of the diagnosis had the next best rates, and those who continued smoking had the worst.[10]

The incidence of lung cancer is reduced 80% to 90% in ex-smokers abstinent for 15 years or more.[1] Of the 12,866 men participating in the Multiple Risk Factor Intervention Trial, no man who never smoked died of lung cancer; the rate per 1,000 person-years was 0.43 for ex-smokers, 0.22 for those who smoked 1 to 19 cigarettes a day, 1.29 for 20 to 39 cigarettes a day, and 1.45 for 40 or more cigarettes a day.[11] When compared with never-smokers, smokers in the US veterans study had a relative risk of lung or bronchial cancer of 11.3, and ex-smokers' relative risk was 4.0.[5] As with many other disease processes in both women and men, those who had previously smoked fewer cigarettes a day, had been abstinent longer, or had stopped for reasons other than illness had generally lower risks.[1,5]

Cardiac Disease

The incidence of cardiac disease and death from coronary heart disease is greatly reduced in those who stop smoking, as reviewed extensively elsewhere.[12] The longer the duration of ex-smoking, the lower the risk of myocardial infarction (MI). In one study of 4,648 men, the age-adjusted relative risk of MI for current smokers versus never-smokers was 2.9; those who had abstained 1 to 2 years had a relative risk of 2.0 when compared with never-smokers; and the relative risk for those who had abstained longer than two years did not differ significantly from that for those who had never smoked ($P \geq .05$), becoming virtually the same as never-smokers' risk by 10 to 20 years of abstinence.[13] Similarly, Rosenberg and colleagues, in their study of 3,285 women, reported that the age-adjusted relative risk of MI for current smokers versus never-smokers was 3.6, that those who had abstained 1 to 23 months had a relative risk of 2.6, and that the relative risk for those who had abstained for longer than 2 to 4 years did not differ significantly from that for those who had never smoked ($P \geq .05$).[14] Those who continue to smoke are clearly at greater risk of MI or death; in the Coronary Artery Surgery Study, smokers had 1.5 times the risk of MI or death that those who quit did (95% confidence interval 1.2 to 1.7).[4]

The risk of death also decreases for those who quit smoking after an MI. The Framingham Study investigators found that the estimated six-year mortality rate was 18.8% for those who quit smoking after their first MI and 30.4% for those who continued.[15] Mulcahy and co-workers reported a five-year mortality of 14.6% for those who stopped smoking following an MI, 14.2% for those who reduced cigarette use, and 28.8% for those who continued their previous levels of use.[16] Goldberg and colleagues found 1-, 5-, and 10-year postmyocardial infarction survival rates of 99%, 97%, and 95% for those who quit smoking and 98%, 84%, and 51% for those who did not.[17]

Vascular Diseases

The risk of stroke for current smokers has been calculated to be 1.5 times that for those who never smoked, with the risk among ex-smokers dropping to 1.2 compared with that for never-smokers. These estimates are based on a meta-analysis of 32 studies.[18] Data also suggest that those who have smoked fewer cigarettes per day and those who have had a longer duration of abstinence from cigarettes are at lower risk for stroke, although the

rate at and the extent to which risk declines are uncertain.[1,5,19,20]

The risk of death from ruptured aortic aneurysm in those who quit smoking appears to be two to three times that in persons who have never smoked but only about half that in those who continue to smoke.[1,5] Former smokers have about half the risk of claudication and peripheral arterial disease as current smokers.[1]

Diseases of Other Organ Systems

In addition to the well-documented benefits of smoking cessation on pulmonary and cardiovascular disease, there is abundant evidence of the value for other organ systems as well. Smoking cessation decreases the risks of peptic ulcer disease, oral, esophageal, bladder, cervical, laryngeal, and pancreatic cancers, and the risk of death from all these diseases.[1,5] Substantial evidence exists that smokers have worse reproductive outcomes, higher risks of osteoporosis, earlier menopause (and hence an increased risk of coronary heart disease in women), more wrinkling,[1] and a higher risk of cataracts[21,22] than do nonsmokers, though there is little direct evidence of the effect of stopping smoking on these outcomes.

Patients often believe that they are merely trading off one disease process for another—that if they do not die of heart disease, they will die of cancer. While this is obviously ultimately true, death is delayed and cancer risk decreased by stopping smoking. In a study by La Croix and co-workers, men who were former smokers had a relative risk for all cancers of 1.7 versus current smokers' relative risk of 2.4; the risk for women who formerly smoked was 1.0 versus current smokers' risk of 2.4.[23]

Additional Risk Factors

Many studies have shown that people often pick clusters of good or poor health habits, although the reason for this is difficult to determine.[1,24] Surveys have shown that former smokers drink alcohol less than do current smokers and more than do those who have never smoked.[1] Two large US studies, the National Health Interview Survey and the Behavioral Risk Factor Surveillance System, have suggested that lack of exercise and smoking may cluster together, as former smokers are less likely to exercise than are those who have never smoked but are more likely to exercise than are current smokers.[1,24]

Substantial evidence exists that smoking adversely affects plasma cholesterol levels.[1,25] The data are strongest for cigarettes' deleterious effect on high-density lipoprotein levels; this has been repeatedly demonstrated in both men[26-29] and women,[27,29,30] and smoking cessation has been shown to lower these levels.[30,31] There is also evidence that smoking adversely affects low-density lipoprotein, very-low-density lipoprotein,[1,26] and triglyceride levels.[26,32] There is direct evidence that smoking cessation improves total cholesterol levels in both men and women.[7,33]

An increase in body weight is the one major health determinant that tends to change in an unhealthy direction after smoking cessation. Smokers tend to weigh less than nonsmokers and to gain weight when they quit smoking.[1,31] The Surgeon General's report summarized 15 prospective studies on smoking and body weight.[1] With a total sample size of 20,217 and a median follow-up of two years, the average weight gain among quitters was 2.1 kg (4.6 lb) versus 0.4 kg (0.8 lb) for continuing smokers. Of those quitting smoking, 79% gained weight versus 56% of continuing smokers. Only 20.3% of quitters versus 10.8% of continuing smokers gained more than 4.5 kg (10 lb), and less than 4% of men or women who quit gained more than 9 kg. Weight gain is probably attributable to a combination of changed food tastes, increased food consumption, and a decreased metabolic rate.[1,12] Much of this weight gain can be avoided through changes in diet and exercise and possibly through the use of nicotine gum—the role of nicotine patches has not yet been tested (see the "Page for Patients" titled "Stopping Smoking: Myths and Reality" at the end of this article). The enormously decreased health risks that occur with smoking cessation eclipse any cessation-induced health risks due to weight gain, however.

Further Effects of Smoking

Often one of the most compelling arguments for a patient to stop smoking is that it is harming others. In the United States about 53,000 persons die each year of passive exposure to tobacco smoke; this includes about 37,000 deaths from heart disease and 3,800 deaths from lung cancer.[34] Most studies have estimated that nonsmoking wives of smokers have an all-cancer risk (as well as a lung cancer risk) that is about 1½ times that of nonsmoking wives with nonsmoking husbands, with a dose-response by number of cigarettes passively inhaled per day.[34,35] Smokers' wives also have an increased incidence of pulmonary epithelial, possibly precancerous, lesions.[9]

Although other cancer risks, in addition to those of lung cancer, that are associated with main-stream smoke also seem to be elevated in those with exposure to side-stream smoke (cancers of the cervix or paranasal sinuses), there may also be some disease risks that are specific to side-stream smoke. It has been speculated that this may be the case for brain and breast cancers in women with exposure to spouses' cigarette smoke and for childhood brain tumors and leukemias associated with parental smoking.[35] Whereas the biologic plausibility of this is unclear, some carcinogenic and other toxic compounds may be present in even higher concentrations in side-stream smoke than in actively inhaled main-stream smoke: particulate matter, nicotine, carbon monoxide, and *N*-nitrosamines, for example.[35]

The pathogenesis of the 37,000 heart disease deaths from passive smoking is also complex. Environmental tobacco smoke may increase platelet adhesion and aggregation and may injure arterial endothelium, all contributing to atherosclerotic plaque formation. Those persons with exposure to side-stream smoke show decreased exertional work capacities and lower chronotropic capacity in response to exercise, and those with preexisting heart disease may even have angina.[34]

Children of smokers are at increased risk for chronic cough and acute respiratory illnesses, for hospital admittance for those illnesses, and for middle ear infections.[35]

Smoking also harms others in less direct ways. In addition to noneconomic costs, the fiscal costs of smoking-attributable fires are about $409 to $616 million a year.[36] Smoking-attributable fires cost employers an estimated $5 to $10 per smoking employee per year. This is, of course, a small portion of the $336 to $601 excess dollars per year that the average smoker costs an employer, $75 to $150 of which is in direct health care costs, $17 to $34 in workers' compensation, $20 to $33 in life insurance, and $40 to $80 in absenteeism.[36]

Other Licit Smoking

In a large (n = 293,958) study of US veterans, cigarette smokers had a relative total mortality of 1.9 compared with those who never smoked; cigar smokers' relative mortality was 1.2 when compared with never-smokers, and for pipe smokers it was 1.1.[5] Risks of death from cardiovascular disease were 1.7 for cigarette smokers, 1.1 for cigar smokers, and 1.0 for pipe smokers; mortality risk from all cancers was 2.2, 1.3, and 1.3, respectively; risk from all respiratory diseases was 4.8, 0.8, and 1.4; and from lung cancer, the risk was 12.1, 1.7, and 2.1.[5] Limited data from this and other studies suggest that mortality from specific diseases such as smoking-related cancers does decrease when persons stop smoking pipes and cigars.[1,5]

Conclusion

The benefits of smoking cessation are unquestionable and have been demonstrated in populations of all ages, in both sexes, in well populations, and in those who have already had a myocardial infarction or have lung cancer. Physicians must become even more active and assertive in recommending smoking cessation to all patients. Less than half of smokers surveyed in two California cities said that they have ever been told to stop smoking by a physician,[37] and similar data have been found elsewhere in the United States.[38] Multiple resources are available to help physicians counsel patients about smoking cessation, such as "The American Academy of Family Physicians' Stop Smoking Kit" (8880 Ward Parkway, Kansas City, MO 64114, [816] 333-9700) and the National Institutes of Health "Clinical Opportunities for Smoking Intervention: A Guide for the Busy Physician."[39] Doing so is every physician's responsibility.

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Stopping Smoking: Myths and Reality

A Page for Patients From The Western Journal of Medicine and Your Doctor

Myth: *Why should I stop smoking? I have to die from something.*

Reality: Sure, you have to die from something. But if you're an average smoker, you're 1½ times as likely to die next year as an ex-smoker of the same age and sex. You're also likely to die three years earlier than an ex-smoker and about twice as likely as an ex-smoker to have a heart attack or to die of cancer.

Myth: *I can't stop smoking, I'll get fat.*

Reality: Chances are, you will gain weight. When smokers quit, 79% of them gain weight, but they gain an average of only 4.6 lb. Exercising, watching what you eat, or using a nicotine replacement like nicotine gum can all help you avoid gaining weight.

Myth: *I just can't enjoy life without cigarettes.*

Reality: Ex-smokers have fewer coughs, better lung function, and a stronger immune system than those who continue smoking. Wouldn't that help you enjoy life?

Myth: *Doesn't cutting down help?*

Reality: Smoking fewer cigarettes does decrease your risks of disease and death. But why would you want these risks to be any higher than they need to be?

Myth: *My aunt Millie smoked 10 packs of cigarettes a day and lived to be 130. Why should I stop?*

Reality: Aunt Millie got lucky. Although the odds were against her, she beat them. It's your choice. Do you prefer to stack the odds for you or against you?

Myth: *I'm already sick from smoking cigarettes. I might as well keep on smoking.*

Reality: Those who quit smoking after a heart attack are 10 times less likely to die as those who continue smoking. Ten years after a heart attack, only 5% of those who quit smoking versus 49% of those who continued smoking had died. People with lung cancer are also much more likely to live if they quit smoking.

Myth: *I'll quit later. My body will still have time to recover.*

Reality: While some unhealthy effects from cigarettes (like those from nicotine) disappear within hours to days after stopping, others take years to clear up. For most diseases caused by cigarettes, the more years you've stopped smoking, the less likely you are to get sick or die.

Myth: *I'm only hurting myself.*

Reality: Not only do your friends and family have to cope with your smoking-related illnesses, you are also increasing their risks of illness and death. In the United States, about 53,000 people die each year of inhaling other people's tobacco smoke. Women who do not smoke but who are married to smokers have a cancer risk 1½ times that of women who are married to nonsmokers. Children exposed to tobacco smoke have more ear infections and lung diseases like pneumonia. Smokers cause $409 to $616 million worth of fires each year, and the average smoker costs an employer between $336 and $601 more a year in health care, workers' compensation, life insurance costs, and absenteeism.

Myth: *I've tried stopping before and failed, so I'll just fail again this time.*

Reality: Lots of people don't succeed right away at stopping smoking. It's a very addictive habit, and many smokers need to try quitting several times before they succeed. Doctors are putting this information into their waiting rooms, though, because they want to help you quit smoking. Ask your doctor to help you quit!

Commentary

Health Decisions Movement

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Many have heard of the Oregon Health Plan, an attempt to allocate scarce medical resources based on current medical knowledge and community health values. Some are acquainted with Oregon Health Decisions, the citizen-based organization that in part developed the plan. Perhaps more have heard of American Health Decisions, the confederation of state health decisions organizations from California to Vermont. I describe the balance of facts and values that underlie setting priorities for the delivery of health care.

The health decisions movement originated as a response to the lack of a fair and prudent health policy in the United States. For example, the simple question "Should more public funds be invested in health promotion relative to those invested in curative medicine?" goes unanswered for the lack of expressed public consensus. In pursuit of balanced health policy, the health decisions movement undertakes to articulate grass roots health values through consensus-seeking community meetings.

Each of 16 affiliated state citizen organizations currently making up the health decisions movement sponsors community meetings, study groups, forums, and literature related to health care delivery. The mission is civic action in health care based on expressed community values. To accomplish this, relevant issues are placed before interested persons for discussion leading to consensus on community values. As consensus develops it becomes the focus of public education and organization directed at constructive health policy. Generally, with consensus on an issue, such as curative versus preventive medicine, the next step is integrating the determined values into the present system by sharing the consensus as well as its relation to relevant issues—cost, treatment procedures, capital investment, populations affected—with policymakers.

The health decisions movement wrestles with important cultural issues such as why health care delivery in our country is such a pressing dilemma while in Canada or most Western European countries, most persons appear reasonably content with their system. The answer turns out to be complex, stemming from two related reasons: In the United States an independent public is actively suspicious of government programs, and the average American has a remarkably strong belief in personal choice.

One complication for the American philosophy of personal independence is a common wish to rescue the unfortunate. Traditionally, regardless of cost, the public is willing to go to extraordinary lengths to rescue a child "trapped down a well." This speaks to an implicit public value for some form of community response.

On the other hand, as a nation we seem much less willing to sacrifice time, money, and emotion for those who suffer unseen, without benefit of outspoken advocates or media hype. To cover this discrepancy between expressed concern and practiced denial, particularly in health care, we assume the government, which from another perspective we view with suspicion, will care for those whose needs, including medical, are less apparent and heartrending. Yet any such government effort, as shown by experience, calls for the setting of priorities in allocating limited health care resources. At this point our rescue philosophy runs counter to our personal choice philosophy.

Confronted with the conflict in values, the public, along with our leaders, fearing an infringement on personal choice, becomes reluctant to undertake any form of explicit setting of priorities for health care allocation. The block comes when the rescue philosophy confounds civic action by swiftly reducing public consideration of priority setting to a matter of deciding life and death. Under such circumstances, so commonly experienced, developing community consensus on priorities demands sophisticated and sustained consideration, or so it seems to the health decisions movement.

The health decisions movement assists the public in clarifying health care values beyond rescue circumstances in relation to larger issues rapidly evolving through medical innovation, a declining economy, an increasing tax burden, and fiercely competing social needs. Here the interplay between facts and values becomes the heartbeat of the health decisions movement.

Every success of the health decisions movement rests on the ability to listen to and appropriately respond to concerned people. We listen in three ways: randomly, to particular groups, and to the community in forum. Perhaps least appreciated is the random listening that has sparked many state health decisions organizations. As concerned persons sharpen their ears to expressed suffering arising from inequities in the delivery of health care, by the inappropriate use of medical technology, or by the waste of valuable resources, they resolve to act. Random

(Crawshaw R: Health decisions movement. West J Med 1993; 159:88-89)

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listening has identified initial cadres of health decisions organizers and workers.

The second way we listen is to existing organizations expressing their concern about mindless or harmful directions health care sometimes takes. We pay attention to actual conditions reported by first-line participants. Voiced distress prompts health decisions organizations to initiate study groups, education programs, and community projects that produce grass roots response available to policymakers and legislators. Valuable information secured in this fashion generally tends to be information and facts about cases and conditions rather than expressed underlying values.

The second way of listening also includes polling the public. Opinion polls have a surprisingly short shelf life, however, largely because responses are not generated by thoughtful discussion and considered reflection of personal values. Knowing that a certain part of the public is in favor of a particular program does little to clarify how this opinion relates to integrated values. In contrast, expressed values, such as those a community places on prenatal care as a considered investment in the future, are more important in determining policy.

The third, and unique, form of listening involves collecting, clarifying, articulating, and carrying community values from public forums. Health decisions organizations organize community meetings offering citizens a forum to voice their health care values. Neighbors can speak and listen. Pertinent questions arise from half-thought-through ideas. Thus critical personal judgments evolve, reflecting deeper principles than could be elicited by passive attendance at an expert's lecture followed by a poll.

At a health decisions forum citizens are not asked if they support or oppose a particular program or aspect of health care. Rather, they are presented with relevant problems, such as whether persons over the age of 75 should receive organ transplants when the cost is high and organs scarce. The goal is not determining the eligibility age for organ recipients but finding out the values the participants use in arriving at their decisions. The search is for an understanding of the basis of their judgments. The value results are then returned to the group to establish a commonality, a consensus, of expressed values.

Our fact-or-value approach, through open community discussion, places the rescue philosophy into a perspective for respectful consideration while preventing it from preempting the work of setting priorities for health care. The question of rescue is transformed into determining how much value the community places on a life jeopardized by a crisis versus a life jeopardized by day-to-day circumstances.

By listening in all three ways, the health decisions movement serves the public's need for participant responsibility in our health delivery system. Only as we clarify, classify, and publish the values of our communities, states, and nation do we enable our political leaders to wisely and carefully weigh expert knowledge with the public's values in establishing health policy. Clarification of community values offers a way through the present maze of conflicting demands and proposals burdening and confusing the delivery of health care.

Editorials

Carotid Endarterectomy—The Big Picture

Wesley Moore, MD, has performed a service by reviewing elsewhere in this issue the carotid endarterectomy trials for the prevention of stroke.[1] His participation in many and leadership in some of those trials have contributed to resolving the controversy that raged through the late 1980s regarding the safety and efficacy of this frequently performed operation. His is a panoramic view spanning the years of initial enthusiasm,[2,3] increasing skepticism[4,5] replaced by nihilism,[6,7] and, finally, vindication of the validity of prophylactic endarterectomy for preventing cerebral infarction in selected symptomatic patients who have stenosis exceeding 70% in the affected carotid artery.[8,9]

From a historical point of view, it is reassuring to consider how an ever-increasing number of physicians has embraced the rigorous demands of the scientific method to demonstrate whether carotid endarterectomy is indeed an effective method for preventing stroke. In the best traditions of the medical art, neurologists and surgeons have joined together to design and carry out, despite acrimonious debate, prospective randomized studies to accumulate compelling data with which to dispel doubt and rancor.

When I participated in the first trials of carotid endarterectomy[10] and anticoagulants[11] for the prevention of stroke following a transient ischemic attack, cooperative studies were just beginning to be undertaken using the then-trail-blazing concepts of control cohorts, multidisciplinary efforts, randomization, careful follow-up, and rigorous statistical analysis.[12,13] From today's vantage point, we were extremely naive, terribly underfinanced, had minimal biostatistical skills, and had far too few cooperating centers with which to accumulate the number of patients necessary for achieving the required power. Furthermore, the studies were conducted in the 1960s before ultrarapid transportation and communication could ensure long-term cohesion among experts from many disciplines in widely dispersed locations, who were not accustomed to cooperative initiatives. For many physicians, the idea of "experimentation" on one's patients was considered to be meddlesome, if not unethical, and patients themselves did not want to be "guinea pigs." Most physicians had been trained to trust their own judgment and not to submit to a random selection of therapy. In this regard, medicine and the public have come a great distance in their general acceptance of the need for evidence produced by trials before accepting new therapies.

The question remains whether the results of these recently reported trials described by Moore will be judged conclusive 20 years hence. For example, the methods used for determining the degree of carotid stenosis in these enormous efforts differ so that they are not directly comparable. In the European Carotid Surgery Trials, arteriographic stenosis is estimated by projecting a line where the normal lumen is thought to have been.[14] This imaginary "measurement" is used as the denominator for determining the degree of stenosis. In contrast, the North American Symptomatic Carotid Endarterectomy Trial began by measuring cross-sectional areas of stenosis but changed midway, recomputed the data, and adopted the simpler equation of linear diameter used by the Veterans Affairs and the Asymptomatic Carotid Atherosclerosis trials.[15-18] Still others use absolute measurements of lumen at the point of the most severe stenosis and reject the use of percentages altogether. Of the group, only the ongoing Asymptomatic Carotid Atherosclerosis study uses hemodynamic changes measured by Doppler ultrasonography for determining hemodynamic stenosis.[19,20] Because of these differences, results of the trials are not directly comparable; yet all purport to give objective, reproducible methods for determining the precise degree of stenosis necessary for surgical intervention—that is, at exactly 70% or greater stenosis, surgical intervention is justified, at 0% to 29% it is not, and in between is not yet known.[8]

What can be learned from a space-satellite view of all such trials, from the earliest ones in the 1960s to the most recent 1990s, for applying our hard-won knowledge to future trials such as carotid angioplasty, tissue plasminogen activator, and other innovative therapies that could supplement or even supplant endarterectomy? The following are key points:

- There must be an equal multidisciplinary partnership among surgeons, neurologists, neuroimaging groups, biostatisticians, and patient coordinators.
- Clinical trials specialists must be responsible for planning, implementing, and overseeing the trial design.
- There must be enough stable funding to sustain the enormous effort required for the acquisition and follow-up of a sufficient number of patients to achieve significance.
- There must be a proper categorization of patients. This can be a vexing problem. For example, in the trials currently ongoing, the definition of asymptomatic has been agreed on as not having had a transient ischemic attack. What constitutes such an attack, however, is enigmatic and subject to many interpretations. Even more difficult is the proper classification of symptomless patients with cerebral infarctions discovered during brain imaging. How should these asymptomatic patients with strokes be classified? There is no unanimity of opinion.
- There must be a built-in mechanism for modifying the trial during its intake phase. This is particularly important if the trial has a several-year accession during which results of other studies or new data or technology that can improve the trial become available. In the past, trial designs seem to have been unnecessarily rigid in this respect.

Despite shortcomings, multidisciplinary, prospective randomized trials represent an enormous advance in clinical research and in the acceptance by the medical com-

munity and the public of the need to subject beliefs based on limited or local experience to the unblinking objectivity of the scientific method.

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A Scientific Basis for Neurologic Rehabilitation

MEDICAL REHABILITATION in the United States was developed at the end of the 19th century by Deforest Willard, MD, an orthopedic surgeon at the Hospital of the University of Pennsylvania. Major expansions of the field have occurred during wartime, especially World War II, in response to the needs of the many soldiers with limb amputations and traumatic injuries of the nervous system. Rehabilitation medicine stressed the need for patients to develop the maximum attainable degree of self-reliance and psychological acceptance of irreversible impairments. The results were of profound benefit to patients, who might otherwise have returned to lives of helplessness and despair. Rehabilitation medicine also influenced other fields, both within and outside of medicine, to take a more humanistic attitude toward the treatment of patients and a broader view of the capabilities of persons with disabilities. But the clinical and research directions of the field became restricted largely to ameliorating symptoms rather than toward attacks on the pathophysiologic mechanisms of nervous system injury. It was recognized that patients suffering stroke or head injury, and some patients with partial spinal cord injuries, can have dramatic functional recoveries, but the mechanisms underlying these recoveries were not known. Many supposed that functional recovery in the first week or two resulted from the resolution of edema, whereas subsequent recovery was due either to behavioral adaptations or to the assumption of lost functions by spared regions of the nervous system. Axons of the central nervous system were thought to be incapable of regeneration. The control of edema became the subject of many therapeutic trials involving corticosteroids, hypothermia, and other modalities. These showed limited success and, in any case, were deemed in the realm of acute-care medicine and not part of the mission of rehabilitation medicine. Theories of delayed recovery suggested that retraining by passive and active manipulations was the logical therapeutic approach, and this became the focus of most rehabilitation programs, as reflected in the name "Physical Medicine."

The scientific investigative scope of the responses of the nervous system to injury has greatly expanded in the past two decades. This should now bring about a reconsideration of the clinical and academic mission of the field of rehabilitation medicine. The article by Bruce Dobkin, MD, in this issue of the journal reviews the progress that has been made in determining the mechanisms of motor recovery following traumatic or ischemic injury to the central nervous system and in devising methods to enhance this recovery.[1] Dr Dobkin notes that whereas evaluations of traditional models of rehabilitation have not documented superiority of one method over another, the application of rehabilitation techniques based on physiologic or pharmacologic studies in animals has yielded some functional improvements in stroke patients and in patients with incomplete spinal cord injuries. These and other approaches that involve manipulations of the injured nervous system by physical, electrical, or pharmacologic interventions are aimed largely at enhancing the activity of spared or partially injured neuronal pathways. They are important to the mission of rehabilitation because, together with behavioral, educational, and sociologic interventions, they have the potential to lead relatively rapidly to improvements in the quality of life for persons with neurologic disabilities. But it would be a mistake to confine the scientific basis for neurologic rehabilitation to such approaches.

Dobkin's review also mentions recent advances in understanding the factors that prevent the regeneration of in-

jured pathways in the mammalian nervous system and the attempts to enhance regeneration by methods aimed at neutralizing these factors. These avenues of investigation must become an integral part of the scientific basis of rehabilitation medicine. Because they are targeted at a reconstitution of the normal anatomic substrate of neurologic function, they have the potential for a far greater therapeutic benefit and should be viewed as a long-term investment for the field of neurologic rehabilitation.[2] The payoff for these approaches is probably not as far off as most have assumed. More than a decade ago, Aguayo and colleagues in Montreal, Quebec, used modern tract tracing techniques to reemphasize that axons of brain and spinal cord neurons have the capacity to regenerate if given an appropriate environment, such as a graft of peripheral nerve.[3] More recently, this group has demonstrated the ability of optic nerve axons to regenerate for long distances in peripheral nerve bridges and to enter the brain, making electrically active synapses with neurons in the optic tectum.[4] The discovery of molecules on the surfaces of oligodendrocytes (the myelin-producing cells of the central nervous system) that cause the collapse of growing tips of regenerating axons[5] has led directly to experimental procedures to enhance regeneration around a partial spinal cord injury through the use of antibodies specific for those inhibitory molecules.[6] Even the role of glial scarring in inhibiting the regeneration of injured axons is being elucidated with the demonstration that reactive glia secrete proteoglycan molecules that repel growing axons.[7] Enzymatic digestion of these proteoglycans neutralizes their inhibitory action in vitro,[8] a finding that should soon lead to attempts to enhance regeneration in vivo. Finally, experimental success in transplanting fetal nervous system tissue into the mature central nervous system in animals has already led to therapeutic trials in which fetal dopaminergic neurons have been introduced into the brains of patients with Parkinson's disease, with early promising results.[9] There is no evidence that the transplanted cells make synaptic connections with host neurons, and it seems likely that they are acting as a semiglandular source of dopamine rather than as participants in a specific neuronal circuit. Fetal transplants are now being tested in experimental spinal cord injury.[10] There has as yet been no evidence for the recovery of lost functions, but when transplanted into neonatal rats and cats, the fetal spinal cord tissue may enhance the development of locomotion.[11,12]

The failure thus far for axonal regeneration to result in the recovery of lost functions should not lead to an abandonment of attempts to further enhance regeneration. The problem may well be largely with the quantity of regenerating axons, which to date has been a small fraction of those injured. Experiments in lower vertebrates, such as lampreys, where growth-inhibiting factors appear to be absent, suggest that axonal regeneration in the spinal cord is specific with regard to both path finding[13] and synaptic reconnection.[14] Thus, if a greater number of axons could be induced to regenerate in the mammalian central nervous system, they might show a tendency to make appropriate connections, which could lead to the restoration of useful function.

These are exciting developments that are ready for intensive follow-up. The prestige of rehabilitation medicine has long suffered from the impression that its scientific base is weak and that its goals are too restricted. Expansion of the research mission into the areas of morphologic as well as physiologic plasticity in the nervous system is the kind of long-term investment that can rejuvenate the field and attract creative minds to it.

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Correspondence

Earthquakes and Myocardial Ischemia

To the Editor: A series of nearby earthquakes, beginning with the Landers, California, tremor (7.5 on the Richter scale) of June 1992 followed by thousands of aftershocks of varying intensity caused apprehension in many of my patients with known coronary artery disease.

A 74-year-old woman was undergoing a Holter monitor study to evaluate recurrent atrial fibrillation when she had an asymptomatic episode of 3.5-mm ST depression at 5:48 AM, June 28, 1992, the same instant as an aftershock graded at 4.2 on the Richter scale (Figure 1). She recalls being slightly apprehensive at that time, but had no specific symptoms. A stress echocardiography was then done that was markedly abnormal, and she underwent coronary arteriography, which showed high-grade, two-vessel coronary disease. She has never had angina pectoris and is being treated with conservative medical management.

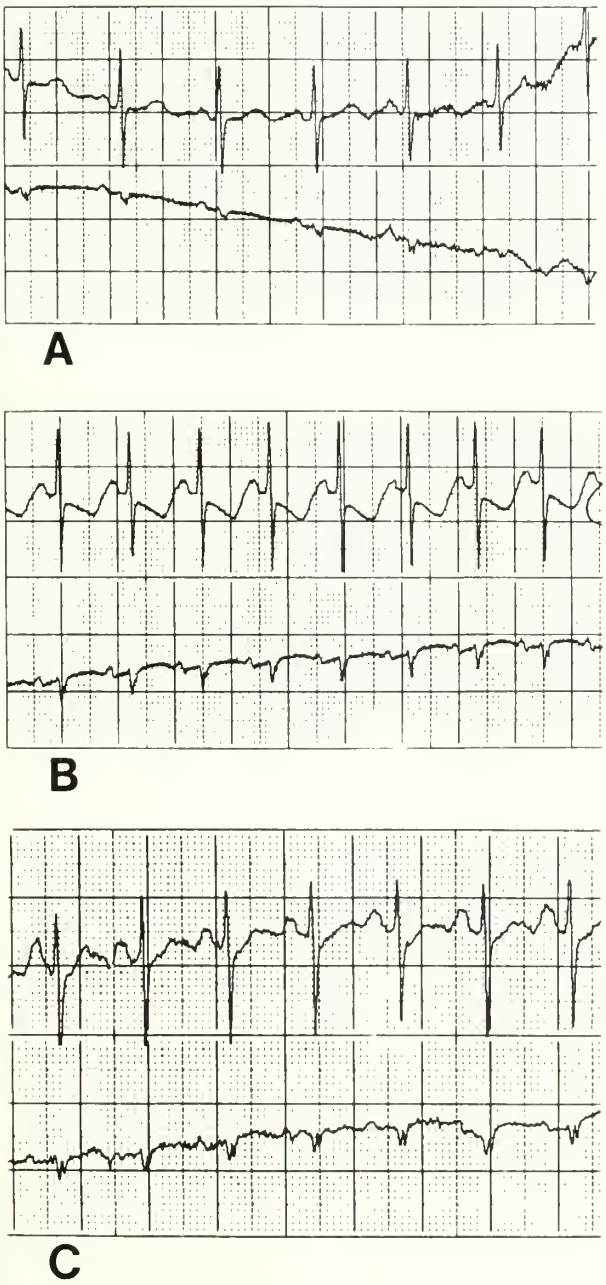

Figure 1.—A 24-hour Holter monitor electrocardiographic study was being done on a 74-year-old woman when an earthquake aftershock occurred that registered 4.2 on the Richter scale. Timed tracings are shown at **(A)** 5:47:59 AM, **(B)** 5:48:15 AM, and **(C)** 5:49:05 AM.

Earthquake-induced stress can increase cardiac mortality.[1] Voridis and colleagues reported cardiac rhythm disturbance measured by Holter monitoring during an earthquake.[2] This may be the first documented case of earthquake-induced (silent) myocardial ischemia.

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High Tech in a Low Tech Country

To the Editor: A 7-year-old boy from a Central American country was seen at the pediatric cardiac clinic at San Francisco General Hospital Medical Center recently holding in his hand a photo of a two-dimensional echocardiogram that purported to show an atrial septal defect. This robust boy's physician had discovered a murmur and referred him for an echocardiogram in his native country that was interpreted as showing a septal defect that needed immediate open heart surgery in the United States.

The family had sold their home and many of their possessions to raise enough money to come to this country for the operation. Along the way, they stopped at the heart clinic, where the clinical findings were more suggestive of a functional murmur. An echocardiogram confirmed that there was no atrial septal or other defect. Apparently the original echocardiographer had misinterpreted the "dropout" that often occurs when viewing the atrial septum with 2D echocardiography as a secundum type defect. Following the revelation that her child's heart was normal, the mother was pensive and anxious. She pointed out that the family had been worried about the boy's heart for a long time, had been convinced that major surgery would be necessary, and therefore found it hard, in a relatively brief period of time, to accept without any doubt the new information that the heart was fine. She needed much reassurance and a letter in her hand stating that all was well before she felt comfortable in returning to a new home in Central America.

The enthusiastic spread of American medical technology to third world countries might be tempered if our colleagues lecturing at national and international medical meetings were more forthcoming about the risks and mistakes that can be made. Otherwise, many more patients will encounter problems similar to those of this little boy and his family.

MARVIN L. AUERBACK, MD
1295 E Hillsdale Blvd
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Testing Cardiac Function

To the Editor: Thank you for the excellent article, "Suggested Guidelines for Rating Cardiac Disability in Workers' Compensation," in the March 1993 issue.[1] A focus on cardiac symptoms of exercise is often ignored, limiting the usefulness of a stress test. A dobutamine hydrochloride echocardiogram, although it does not provide a met level, can be a useful substitute to assess both coronary insufficiency and cardiac function during exercise.

HUGH F. HAEGELIN, MD
399 E Highland Ave, Ste 220
San Bernardino, CA 92404-3881

REFERENCE

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* * *

Dr Markovitz Responds

To the Editor: Dr Haegelin has suggested a dobutamine echocardiogram as an additional useful test to assess both coronary insufficiency and cardiac function during exercise. He is correct. Many other tests can be used to assess cardiac disability. The purpose of our guidelines was to provide a rational and reasonable system without going into numerous expensive tests.

A dobutamine echocardiogram would be useful, especially in patients who could not exercise, but many other tests might be used. We think that if a test outside the guidelines is used, it should be fully justified and conform to the spirit of cost control.

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An Offshore Pharmacy—A Bargain or a Danger?

To the Editor: With the continuing upward spiral of medical care and prescription drug costs, persons on limited incomes are experiencing great difficulty in paying for life-saving medications. So it is not surprising that someone would come along to offer a convenient discount drug service. And no prescription is necessary.

Medicine Club International, advertising itself as an "international pharmacy," claims to save the buyer up to 60% on costly name-brand medications by importing European and Canadian generic equivalents. Purportedly, they obtain medicines from countries with regulated prices as well as from manufacturing sources that do not observe pharmaceutical patent laws.

By simply telephoning an 800 number, anyone can purchase by credit card or cashier's check a myriad of medications from a formulary of 85 popular prescription drugs. The toll-free number connects the buyer to an English-speaking person in the Bahamas. While the customer is informed that all products are generic equivalents, the manufacturing sources are not disclosed. Although a prescribing physician's name is requested, no written prescription or other documentation is required to receive the medicine.

Only after payment is received in the Bahamas are the items shipped separately, not from the Bahama Islands but from Canada. To conceal the real nature of the shipment, a flat, unlabeled blister pack of 100 individually packaged tablets is sent by ordinary mail in plain business-sized envelopes with no return address. An accompanying invoice, with no product expiration date or product source data, instructs the buyer to "TAKE ALL MEDICATION AS DIRECTED BY YOUR PHYSICIAN."

It does not take a professor of medicine to figure out that Medicine Club International is illegally dispensing medications and is endangering the health and lives of bargain-hunting United States citizens. Potent antihypertensive and cardiac agents, psychiatric drugs, immunosuppressive and anticancer treatments, antibiotics, and hormones can be purchased without any medical or regulatory control. While the potency and purity of the products may be as advertised, there is no evidence that these drugs were manufactured under strict quality controls.

A sales brochure emphasizes that "Drug prices are exorbitant because patents prevent competition." But are their generic equivalents such good buys? As an example, Medicine Club's 400 mg ibuprofen lists at $12 for 100 tablets. In contrast, 500 generic ibuprofen tablets of identical strength manufactured in the United States can be purchased from a wholesaler for $9.95 (suggested retail, $19.90 for 500 tablets).

Although foreign-made medicines may be purchased overseas for personal use, travelers are required to carry them through and identify them to US Customs officials on arrival. The clandestine mailing of prescription drugs across international borders is strictly forbidden by US and foreign postal, customs, and food and drug regulations.

This illegal "international pharmacy" is not the first of such offshore clandestine operations. While Medicine Club International could be closed by seizing the Bahama Islands mail drop, disconnecting the toll-free telephone lines, or by canceling the merchant's credit card account, this will not eliminate these surreptitious schemers. The cooperation of government agencies, the pharmaceutical

industry, and the medical and pharmacy professions is needed. Meanwhile, the medical community should be encouraged to warn its patients of the dangers of taking illegally obtained medications as well as to notify regulatory agencies and the public when they become aware of these operations.

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The Editors are pleased to receive letters commenting on articles published in the journal in the past six months, as well as information or short case reports of interest to our readers. ALL MATERIAL SUBMITTED FOR CONSIDERATION MUST BE DOUBLE-SPACED. Letters NO LONGER THAN 500 WORDS are preferred. An original typescript and one copy should be submitted. All letters are published at the discretion of the Editors and subject to appropriate editing. Those of a scientific nature will be peer reviewed. Authors should include information regarding conflict of interest, when appropriate ("I warrant that I have no financial interest in the drugs, devices, or procedures described in this letter"). Most letters regarding a previously published article will be sent to the authors of the article for comment. Authors of accepted letters will have an opportunity to review the edited version before publication.

Lessons From the Practice

House Calls and Ice Cream

STUART L. SHEAR, MD
Los Angeles, California

I CAN REMEMBER sitting in the back of my dad's 1953 Pontiac, wearing flannel pajamas and sparring with my sister over the exact location of the midpoint of the back seat. My dad was taking us with him on another house call. He had this big chrome floodlight that he would plug into the cigarette lighter as he approached the correct street. Using it, he would lean over and squint to view the addresses as he inched along from one tract home to the next. He would always say, "I'll be right back." And we would always reply, "Please don't be long, Daddy."

An interminable amount of time would pass as the two of us sat in that locked car somewhere in the San Fernando Valley night. Sometimes my dad would take so long, he would come out and find the two of us in tears. He would feel terrible and say, "I wasn't really that long, was I?" We would insist, "Yes, you were!" and busy ourselves wiping the tears from our eyes with the backs of our hands.

Our usual payment for an extra long wait in the car was a visit to the ice cream parlor for a hot fudge sundae.

"How much did they pay you, Daddy?" and "What did they have?" we would ask as we drove off in anticipation of our ice cream. Dad would answer the first question by pulling out a crisp $10 bill from his shirt pocket. In answering the second question, he would make no attempt to simplify technical medical terms. He would say, "nephritis," or "angina," or "status postmyocardial infarction." We would just reply, "Oh."

Growing up in our house, with my dad, made it easy to understand his concept of medical economics. Although he never discussed the issue, his feelings were clear: Practicing medicine should provide you with enough money to raise your family in a safe neighborhood, put your kids through college, and take the family on a vacation for one or two weeks a year. He truly loved his work, and, somewhat unwillingly, he retired when his office landlord wanted him to sign a long-term lease at the age of 72.

I now practice medicine as a dermatologist. In my office, in the small room where I do my laboratory work, there is a photograph of my dad hanging on the wall. It was taken over 40 years ago, and it has those familiar, broad venetian blinds in the background that were so popular then. Looking into Dad's soft eyes, I get a comfortable, warm feeling. I am reminded how lucky I am to have chosen such a wonderful profession.

(Shear SL: House calls and ice cream. West J Med 1993; 159:96)

Dr Shear is in private practice in dermatology and dermatologic surgery in Los Angeles, California.

Reprint requests to Stuart L. Shear, MD, 1245 Wilshire Blvd, Ste 907, Los Angeles, CA 90017.

A $20 Life

KURT B. NOLTE, MD
Albuquerque, New Mexico

THE SOUND OF GUNFIRE was not unusual in the drug-ridden neighborhood. The car lurched forward and stopped against a utility pole, a young man slumped over the steering wheel. A woman exited the front passenger door and fled down the street. Then, all was quiet.

Birth and death are the coinage of existence. In my practice as a forensic pathologist, violent deaths are a common occurrence. Despite their frequency, I am still amazed by the often trivial precipitants. A man once shot his wife and daughter because they had persisted in serving him pork chops, which he could not chew because he lacked teeth. Another man shot his best friend in a drunken argument over how many dams there were on the lake where they were fishing. Life is cheap. Nowhere is this more obvious than in the competitive "business environment" of drug dealing.

I examined the young man from the automobile in the stillness of the autopsy room that Saturday morning and noted a small round entrance gunshot wound over the left temple. A simple hole. Surrounding the wound were the punctate abrasions of gunpowder stippling. "It's an intermediate-range gunshot wound," I told the detective, "a distance generally less than 2 to 3 feet."

The detective narrated briefly the story given by the woman passenger, who was a prostitute. The young man was a corrections officer who had just received his weekly paycheck. To celebrate with a night on the town, he first picked up the young woman. Together they drove to another neighborhood to purchase some cocaine. The young man circled a block several times while pricing the drug with various curbside dealers. He eventually settled into negotiations with one dealer and agreed to purchase 11 bags of cocaine at $20 a bag. He pulled a wad of $20 bills from his wallet, counted out 11, and handed them out through the window into the darkness, to the dealer. The dealer handed him the cocaine and counted his money. "Hey, man! I'm short $20," he exclaimed. "No you're not, I gave you 11 twenties," replied the young man. The argument lasted ten seconds until a supervising dealer stepped forward from against a building. "What's happening?" "He shorted me $20," said the curbside dealer. "Shoot him," authorized the more senior partner.

The detective had been at the death scene earlier in the morning, before the autopsy. I asked him what he had observed. "Not much, Doc. Just a $20 bill in the gutter."

(Nolte KB: A $20 life. West J Med 1993; 159:96)

From the Office of the Medical Investigator, University of New Mexico School of Medicine, Albuquerque.

Reprint requests to Kurt B. Nolte, MD, Office of the Medical Investigator, University of New Mexico School of Medicine, Albuquerque, NM 87131.

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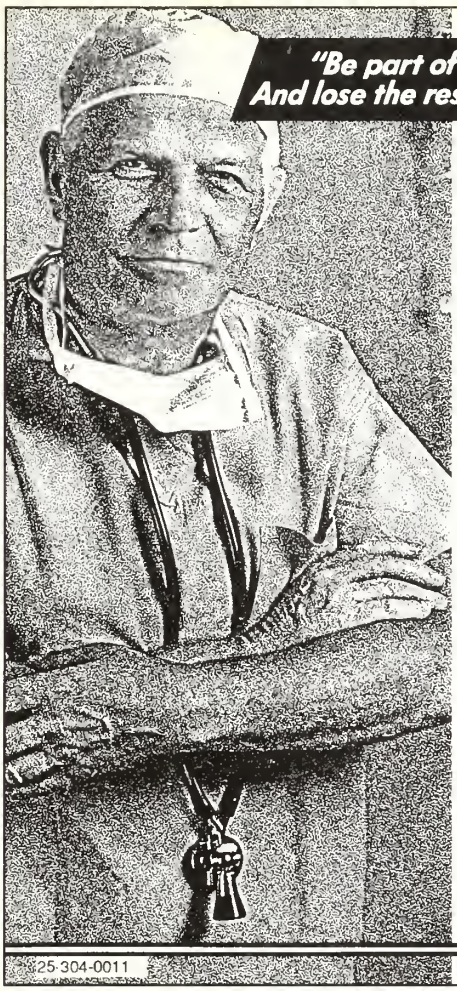

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NATIONWIDE TRAVEL. Health research organization seeks physician for National Health and Nutrition Examination Survey sponsored by the US Public Health Service. Individual will be part of a large medical team conducting health examinations in government mobile exam centers traveling to 88 areas of the US through Fall of 1994. Must be licensed in one state. One year minimum commitment and full-time continuous travel required. Competitive salary, paid malpractice, per diem, car, four weeks paid vacation per year, holidays, and health, life, dental, disability insurance offered. Call Beverly Geline, (800) 937-8281, ext 8248. Westat, Inc, Rockville, MD. EOE/M/F/V/H.

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California Forensic Medical Group, Inc, a private corporation providing medical and dental services to the Stanislaus county correctional facilities in Modesto, California, is seeking a full-time physician with a specialty in Internal Medicine/Family Practice or Emergency Room. Responsibilities would include treatment of patients, supervision of mid-level practitioners and assisting the Medical Program Manager with Quality Assurance. Position offers competitive salary, paid malpractice insurance and additional pay for on-call services. **Contact Elaine Hustedt at (408) 422-0214 or send CV to Elaine Hustedt, PO Box 1011, Salinas, CA 93902.**

(Continued on Page 100)

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PHYSICIANS WANTED

PACIFIC NORTHWEST OPPORTUNITIES

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Northwest Permanente, P.C., is seeking a Board Certified or Eligible Internist, Pediatrician or Family Physician to cover the clinical practice of physician colleagues who are on sabbatical, parental leave, or other long-term leave. Our multi-specialty group is comprised of 540 physicians who provide a full range of services to 380,000 members of Kaiser Permanente in primarily the Portland metropolitan area. We have two full-service hospitals and 11 primary care clinics in addition to six other clinics in the region.

Northwest Permanente offers a professionally stimulating environment and a competitive salary/benefit package which includes professional liability coverage, family medical/dental insurance, two pension programs, and other benefits. **For more information, please contact Judy Parmenter, Professional Staff Recruiter at (503) 721-3874, or forward inquiry with C.V. to: W. J. Weiland, M.D., Regional Medical Director, NORTHWEST PERMANENTE, P.C., 2701 N.W. Vaughn St., Ste. 300, Portland, OR 97210-5398. EOE.**

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ENJOY THE GREAT SOUTHWEST. Thomas-Davis Medical Centers, an expanding multispecialty group of 190 plus physicians, needs BC/BE Pediatrics, Internal Medicine, Family Practice, OB/GYN, Urgent Care, Urology, General Surgery, Psychiatry, and Hematology/ Oncology physicians. Top benefits, profit sharing, guarantee first two years, plus incentive pay, early shareholder. Fee-for-service plus HMO. Call or write TDMC/CPR, (800) 658-9166, TDMC, PO Box 12650, Tucson, AZ 85732.

INTERNIST/FAMILY PRACTICE. Physicians for well loved multidisciplinary Geriatric health center. Part of east San Francisco bay area community clinic network. Permanent and locum tenens positions available. 50-80% time Participation in hospital and call coverage desired. Resident teaching and UCSF clinical affiliation possible. Call (510) 644-6060.

MAJESTIC SKAGIT VALLEY IN WESTERN WASHINGTON has multispecialty group seeking eighth Family Practitioner BC/BE, OB optional. Competitive salary and benefits. If interested, send CV to Shane Spray, 1400 E Kincaid, Mount Vernon, WA 98273.

URGENT CARE. WASHINGTON STATE. Urgent Care Center within 30 physician group seeks physician desiring practice with reasonable hours and workload. Located in the foothills of the Blue Mountains with nationally recognized liberal arts college, superb community symphony, excellent public schools, and plentiful recreational opportunities, including skiing, nearby. Guar-anteed salary with incentive, excellent benefits, and retirement plans. CV to Administrator, Walla Walla Clinic, 55 W Tietan, Walla Walla, WA 99362.

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ARIZONA. Hospital sponsored solo opportunities for Family Practitioners and Internists. Excellent compensation with ample coverage. Well-equipped facility including MRI and CT. Send CV or contact Mitch Young, PO Box 1804, Scottsdale, AZ 85252; (602) 990-8080; FAX (602) 990-8513.

MONTEREY, CALIFORNIA. BC/BE Internist needed to replace retiring partner in busy four member group. Reply to Number 273, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

OB/GYN. Multispecialty group in northwest Washington desires second Obstetrician. Excellent practice opportunity, full range of benefits, early partnership status, all practice costs paid For more information contact Shane Spray, 1400 E Kincaid, Mount Vernon, WA 98273; (206) 428-2524.

(Continued on Page 101)

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SUMMIT HEALTH Ltd.

(Continued from Page 100)

OTOLARYNGOLOGIST. BC/BE to join 28 physician multispecialty group practice. Located in beautiful Pacific northwest between Seattle and Vancouver, BC. Contact Shane Spray, 1400 E Kincaid, Mount Vernon, WA 98273.

EXCELLENT OPPORTUNITY FOR INTERNAL MEDICINE PHYSICIAN in private practice multispecialty physician group in San Francisco. Income guarantee. No investment. Forward CV to Box 263, The Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602

WASHINGTON. Openings for career oriented Emergency Physicians, BC in Emergency or Primary medical specialty. Seattle metropolitan hospital with 54,000 annual visits. Excellent salary in a stable growing group. Contact Maurice Montag in care of Tammie Johnson, 8009 S 180th, Ste 103, Kent, WA 98032, (206) 575-2595.

BC/BE FAMILY PRACTITIONER with interest in OB and a commitment to caring for the underserved, needed to join clinics in Hermiston, Oregon. Diverse cultural influences. Rural setting, abundant recreational opportunities. Competitive salary, Public Health Service loan repayment slots, professional liability, excellent benefit package including vacation up to 32 days per year. Contact Ann Garza, Director of Personnel, or Sylvan Robb, Recruiting Specialist, at (509) 865-5898.

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Highly respected, 35 member multispecialty group seeks second Medical Oncologist to join a busy, regional practice. Group is site for CCOP protocols and practices out of one of Oregon's premier hospitals which is seeking a quarter-time Medical Director for its cancer programs. Portland offers an outstanding quality of life near mountains and the ocean. **Call Pat Wall; (800) 462-1857.**

SEATTLE. Pacific Medical Center and Clinics has Family Practitioner BC/BE positions available at three of its six neighborhood clinics. PMC is a large multispecialty nonprofit organization affiliated with the University of Washington. Our patient population includes retired military personnel and their families, managed care patients involved in PPOs and HMOs, and fee-for-service patients. Most of our well run, well equipped clinics are located within one mile of a major hospital. PMC offers its providers a balanced lifestyle, competitive salaries and an excellent benefit package that includes a competitive salary, pension plan, bonus plan, paid malpractice, plus much more. Come enjoy the Puget Sound area with all it has to offer. Send CV to Marilyn Gosanko, Employment Manager, Pacific Medical and Clinics, 1200 12th Ave S., Seattle, WA 98144, (206) 326-4111. EOE

MEDICAL DIRECTOR. Monterey Bay 230-bed hospital in the heart of Steinbeck country is actively seeking an MD interested in a management role as the administration liaison to the medical staff. Requirements include proven communication skills, minimum five years clinical practice experience, working knowledge of managed care contracting, governmental regulations, UR/QA, credentialing, and planning. If you are a team player with the desire and ability to lead a quality medical staff into the '90s, contact Ken Baker, Baker Group, 550 Montgomery St, Ste 725, San Francisco, CA 94111; (800) 229-0411 or FAX (415) 399-0411

MEDICAL DIRECTOR. FAMILY PRACTICE/INTERNAL MEDICINE. Experienced Primary Care physician sought for Medical Director of Santa Clara County Adult Correctional Facility. Clinical and administrative duties required in an outpatient setting affiliated with Santa Clara Valley Medical Center. Requires supervision of physicians and Nurse Practitioners, maintenance of accreditation standards. Should be familiar with outpatient management of HIV related disorders. Competitive salary, excellent benefits. Send CV to Phillip M. Benaron, MD, Medical Administration, 751 S Bascom Ave, San Jose, CA 95128, or call (408) 299-5105

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(Continued on Page 102)

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WE VALUE YOUR SKILLS IN THE PACIFIC NORTHWEST. Do you practice Obstetrics? Have Spanish language skills? Do you enjoy working with underserved populations? Community and migrant health centers in Alaska, Idaho, Oregon, and Washington have diverse opportunities for Family Physicians in urban and rural areas, some including loan repayment. Practice where it's nearly perfect. Send CV to NWRPCA, 4154 California Ave SW, #7, Seattle, WA 98116, (206) 932-2133.

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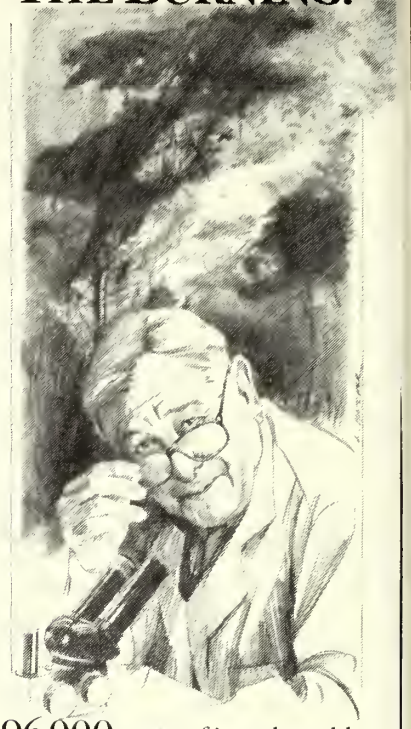
FAMILY PRACTICE. Premier multispecialty group near Portland, Oregon has two excellent opportunities for BC/BE Family Practitioners. Join one of two satellite clinics in which Family Physicians and Physician Assistants currently practice. Superb lifestyle, abundant recreational opportunities, and generous benefits package. Send CV to Karen Stanton, c/o The Vancouver Clinic, 700 NE 87th Ave, Vancouver, WA 98664.

SAN FRANCISCO BAY AREA. PALO ALTO MEDICAL CLINIC, a 150 physician multispecialty group noted for innovation and excellence seeks full-time physician for Occupational Medicine practice. Physicians with BC in Occupational Medicine, Family Practice, or Emergency Medicine preferred. Practice environment, salary, and benefits are unexcelled. Two year partnership track. Please forward letter of interest and résumé to George Perlstein, MD, Medical Director, Palo Alto Medical Clinic, 300 Homer Ave, Palo Alto, CA 94301.

ORTHOPEDIC SURGEONS. Orthopedic Surgeon for a very busy Orthopedic service in a 223-bed teaching hospital with residencies in General Surgery, Internal Medicine, OB/GYN, and Family Practice. Should be BC/BE. Experience in arthroscopy preferred. Salary and compensation plan negotiable depending on experience. Hospital located in beautiful northern San Joaquin Valley close to major cities and skiing areas. Please submit CV and references or contact Nathaniel Matolo, MD, Chief of Surgery, San Joaquin General Hospital, PO Box 1020, Stockton, CA 95201; phone (209) 468-6600. AA/EOE.

(Continued on Page 103)

IT'S TIME TO STOP THE BURNING.



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Rain Forest Rescue.

The National Arbor Day Foundation

Call Rain Forest Rescue NOW.
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(Continued from Page 102)

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NORTHWEST PERMANENTE, P.C., has two excellent opportunities for Board Certified or Eligible General Internists to join our 16-physician primary care group in Longview-Kelso, Washington, a picturesque, stable community of 42,000 people. A full range of professional services are provided to Kaiser Permanente's 26,000 plan members in the area.

We offer a competitive salary and benefit package which includes two comprehensive pension plans, paid professional liability and sabbatical leave. **Forward C.V. and inquiry to: W.J. Weiland, M.D., Regional Medical Director, NORTHWEST PERMANENTE, P.C., 2701 N.W. Vaughn St., Ste. 300, Portland, OR 97210-5398. EOE.**

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Western States OPENINGS

Many multispecialty groups and hospitals have asked us to recruit for over 300 positions of various specialties. Both permanent and locum tenens. Send CV to **Western States Physician Services, 5627 E. Kings Canyon, Ste 156, Fresno, CA 93727, or call (800) 873-0786.**

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HEALTH OFFICER. Lake County, California seeks qualified physician for role of Health Officer pursuant to Health and Safety Code Section 451, via part-time contract. For further information, contact Robert Erickson, LCSW, MPA, Director of Health Services, 922 Bevins Ct, Lakeport, CA 95453; (707) 263-8929, FAX (707) 263-1662.

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ROCKY MOUNTAIN WEST AND SOUTHWEST NEED PHYSICIANS. All specialties needed. Urban, rural, solo, group opportunities, all close to mountain recreation. Call Rita Longino at (800) 279-5267 or FAX CV to (800) 467-1246 or send CV to WHS, PO Box 2107, Corrales, NM 87048-2107.

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(Continued on Page 106)

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California Medical Association—PO Box 7690, San Francisco 94120-7690. (415) 541-0900. Annual Meeting: March 18-23, 1994, Disneyland Hotel, Anaheim.

Colorado Medical Society—PO Box 17550, Denver 80217-0550. (303) 779-5455. Annual Meeting: September 10-12, 1993, Snowmass Village, Snowmass.

Hawaii Medical Association—1360 S Beretania, Honolulu 96814. (808) 536-7702. Annual Meeting: October 9-11, 1993, Ritz Carlton Kapalua, Maui.

Idaho Medical Association—305 W Jefferson, PO Box 2668, (208) 344-7888. Annual Meeting: July 29-31, 1993, Sun Valley.

Montana Medical Association—2012 11th Ave, Suite 12, Helena 59601. (405) 443-4000. Annual Meeting: September 30-October 2, 1993, Butte.

Nevada State Medical Association—3660 Baker Lane, Reno 89502. (702) 825-6788. Annual Meeting: April 21-24, 1994, Coronado, California.

New Mexico Medical Society—7770 Jefferson NE, Suite 400, Albuquerque 87109. (505) 828-0237. Annual Meeting: 1994, date and location to be announced.

Utah Medical Association—540 E Fifth South, Salt Lake City 84102. (801) 355-7477. Annual Meeting: September 22-25, 1993, University Park Hotel, Salt Lake City.

Washington State Medical Association—900 United Airlines Bldg, 2033 6th Ave, Seattle 98121. (206) 441-WSMA. Annual Meeting: September 9-12, 1993, Jantzen Beach, Oregon.

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For The Treatment Of Reflux Disease

WHEN ACID REFLUX ERUPTS

Zantac® 150 Tablets
(ranitidine hydrochloride)

Zantac® 300 Tablets
(ranitidine hydrochloride)

Zantac® Syrup
(ranitidine hydrochloride)

BRIEF SUMMARY

The following is a brief summary only. Before prescribing, see complete prescribing information in Zantac® product labeling.

INDICATIONS AND USAGE: Zantac® is indicated in:
1. Short-term treatment of active duodenal ulcer
2. Maintenance therapy for duodenal ulcer patients at reduced dosage after healing of acute ulcers
3. The treatment of pathological hypersecretory conditions (e.g., Zollinger-Ellison syndrome and systemic mastocytosis)
4. Short-term treatment of active, benign gastric ulcer
5. Treatment of gastroesophageal reflux disease (GERD)
6. Treatment of endoscopically diagnosed erosive esophagitis.

Concomitant antacids should be given as needed for pain relief to patients with active duodenal ulcer; active, benign gastric ulcer; hypersecretory states; GERD, and erosive esophagitis

CONTRAINDICATIONS: Zantac® is contraindicated for patients known to have hypersensitivity to the drug or any of the ingredients

PRECAUTIONS: General: 1. Symptomatic response to Zantac® therapy does not preclude the presence of gastric malignancy
2. Since Zantac is excreted primarily by the kidney, dosage should be adjusted in patients with impaired renal function (see DOSAGE AND ADMINISTRATION). Caution should be observed in patients with hepatic dysfunction since Zantac is metabolized in the liver.
3. Rare reports suggest that Zantac may precipitate acute porphyric attacks in patients with acute porphyria. Zantac should therefore be avoided in patients with a history of acute porphyria.

Laboratory Tests: False-positive tests for urine protein with Multistix® may occur during Zantac therapy, and therefore testing with sulfosalicylic acid is recommended

Drug Interactions: Although Zantac has been reported to bind weakly to cytochrome P-450 *in vitro*, recommended doses of the drug do not inhibit the action of the cytochrome P-450-linked oxygenase enzymes in the liver. However, there have been isolated reports of drug interactions that suggest that Zantac may affect the bioavailability of certain drugs by some mechanism as yet unidentified (e.g., a pH-dependent effect on absorption or a change in volume of distribution)

Increased or decreased prothrombin times have been reported during concurrent use of ranitidine and warfarin. However, in human pharmacokinetic studies with dosages of ranitidine up to 400 mg per day, no interaction occurred, ranitidine had no effect on warfarin clearance or prothrombin time. The possibility of an interaction with warfarin at dosages of ranitidine higher than 400 mg per day has not been investigated

Carcinogenesis, Mutagenesis, Impairment of Fertility: There was no indication of tumorigenic or carcinogenic effects in life-span studies in mice and rats at dosages up to 2,000 mg/kg per day

Ranitidine was not mutagenic in standard bacterial tests (*Salmonella, Escherichia coli*) for mutagenicity at concentrations up to the maximum recommended for these assays.

In a dominant lethal assay, a single oral dose of 1,000 mg/kg to male rats was without effect on the outcome of two matings per week for the next 9 weeks.

Pregnancy: ***Teratogenic Effects: Pregnancy Category B:*** Reproduction studies have been performed in rats and rabbits at doses up to 160 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to Zantac. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed

Nursing Mothers: Zantac is secreted in human milk. Caution should be exercised when Zantac is administered to a nursing mother

Pediatric Use: Safety and effectiveness in children have not been established

Use in Elderly Patients: Ulcer healing rates in elderly patients (65-82 years of age) were no different from those in younger age-groups. The incidence rates for adverse events and laboratory abnormalities were also not different from those seen in other age-groups

ADVERSE REACTIONS: The following have been reported as events in clinical trials or in the routine management of patients treated with Zantac®. The relationship to Zantac therapy has been unclear in many cases. Headache, sometimes severe, seems to be related to Zantac administration

Central Nervous System: Rarely, malaise, dizziness, somnolence, insomnia, and vertigo. Rare cases of reversible mental confusion, agitation, depression, and hallucinations have been reported, predominantly in severely ill elderly patients. Rare cases of reversible blurred vision suggestive of a change in accommodation have been reported. Rare reports of reversible involuntary motor disturbances have been received.

Cardiovascular: As with other H_2-blockers, rare reports of arrhythmias such as tachycardia, bradycardia, atrioventricular block, and premature ventricular beats.

Gastrointestinal: Constipation, diarrhea, nausea/vomiting, abdominal discomfort/pain, and rare reports of pancreatitis.

Hepatic: In normal volunteers, SGPT values were increased to at least twice the pretreatment levels in

Zantac® 150 and 300 (ranitidine hydrochloride) Tablets
Zantac® (ranitidine hydrochloride) Syrup

6 of 12 subjects receiving 100 mg q.i.d. intravenously for 7 days, and in 4 of 24 subjects receiving 50 mg q.i.d. intravenously for 5 days. There have been occasional reports of hepatitis, hepatocellular or hepatocanalicular or mixed, with or without jaundice. In such circumstances, ranitidine should be immediately discontinued. These events are usually reversible, but in exceedingly rare circumstances death has occurred

Musculoskeletal: Rare reports of arthralgias and myalgias

Hematologic: Blood count changes (leukopenia, granulocytopenia, and thrombocytopenia) have occurred in a few patients. These were usually reversible. Rare cases of agranulocytosis, pancytopenia, sometimes with marrow hypoplasia, and aplastic anemia and exceedingly rare cases of acquired immune hemolytic anemia have been reported

Endocrine: Controlled studies in animals and man have shown no stimulation of any pituitary hormone by Zantac and no antiandrogenic activity, and cimetidine-induced gynecomastia and impotence in hypersecretory patients have resolved when Zantac has been substituted. However, occasional cases of gynecomastia, impotence, and loss of libido have been reported in male patients receiving Zantac, but the incidence did not differ from that in the general population

Integumentary: Rash, including rare cases suggestive of mild erythema multiforme, and, rarely, alopecia.

Other: Rare cases of hypersensitivity reactions (e.g., bronchospasm, fever, rash, eosinophilia), anaphylaxis, angioneurotic edema, and small increases in serum creatinine

OVERDOSAGE: There has been limited experience with overdosage. Reported acute ingestions of up to 18 g orally have been associated with transient adverse effects similar to those encountered in normal clinical experience (see ADVERSE REACTIONS). In addition, abnormalities of gait and hypotension have been reported

When overdosage occurs, the usual measures to remove unabsorbed material from the gastrointestinal tract, clinical monitoring, and supportive therapy should be employed

Studies in dogs receiving dosages of Zantac® in excess of 225 mg/kg per day have shown muscular tremors, vomiting, and rapid respiration. Single oral doses of 1,000 mg/kg in mice and rats were not lethal. Intravenous LD_{50} values in mice and rats were 77 and 83 mg/kg, respectively

DOSAGE AND ADMINISTRATION: (See complete prescribing information in Zantac® product labeling.)

Active Duodenal Ulcer: The current recommended adult oral dosage is 150 mg or 10 mL (2 teaspoonfuls equivalent to 150 mg of ranitidine) twice daily. An alternative dosage of 300 mg or 20 mL (4 teaspoonfuls equivalent to 300 mg of ranitidine) once daily at bedtime can be used for patients in whom dosing convenience is important. The advantages of one treatment regimen compared to the other in a particular patient population have yet to be demonstrated

Maintenance Therapy: The current recommended adult oral dosage is 150 mg or 10 mL (2 teaspoonfuls equivalent to 150 mg of ranitidine) at bedtime

Pathological Hypersecretory Conditions (such as Zollinger-Ellison syndrome): The current recommended adult oral dosage is 150 mg or 10 mL (2 teaspoonfuls equivalent to 150 mg of ranitidine) twice a day. In some patients it may be necessary to administer Zantac® 150-mg doses more frequently. Dosages should be adjusted to individual patient needs, and should continue as long as clinically indicated. Dosages up to 6 g per day have been employed in patients with severe disease

Benign Gastric Ulcer: The current recommended adult oral dosage is 150 mg or 10 mL (2 teaspoonfuls equivalent to 150 mg of ranitidine) twice a day

GERD: The current recommended adult oral dosage is 150 mg or 10 mL (2 teaspoonfuls equivalent to 150 mg of ranitidine) twice a day

Erosive Esophagitis: The current recommended adult oral dosage is 150 mg or 10 mL (2 teaspoonfuls equivalent to 150 mg of ranitidine) four times a day

Dosage Adjustment for Patients With Impaired Renal Function: On the basis of experience with a group of subjects with severely impaired renal function treated with Zantac, the recommended dosage in patients with a creatinine clearance less than 50 mL per minute is 150 mg or 10 mL (2 teaspoonfuls equivalent to 150 mg of ranitidine) every 24 hours. Should the patient's condition require, the frequency of dosing may be increased to every 12 hours or even further with caution. Hemodialysis reduces the level of circulating ranitidine. Ideally, the dosing schedule should be adjusted so that the timing of a scheduled dose coincides with the end of hemodialysis.

July 1992
2130B

Glaxo Pharmaceuticals
DIVISION OF GLAXO INC

Zantac® 150 Tablets/Zantac® 300 Tablets
Glaxo Pharmaceuticals, Research Triangle Park, NC 27709

Zantac® Syrup:
Manufactured for Glaxo Pharmaceuticals, Research Triangle Park, NC 27709
by Roxane Laboratories, Inc., Columbus, OH 43216

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Zantac® Tablets

ranitidine HCl/Glaxo 150 mg tablets bid

For The Treatment Of Reflux Disease

WHEN ACID REFLUX ERUPTS

Please see Brief Summary of Prescribing Information on adjacent page.

Glaxo/ Roche

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Second Class

A Clear Refinement In The Treatment Of Depression

ONCE-DAILY

PAXIL™ 20 MG

PAROXETINE HCl

SmithKline Beecham Pharmaceuticals

Please see brief summary of prescribing information on adjacent page.

Philadelphia, PA 19101 © SmithKline Beecham, 1993

ONCE-DAILY
PAXIL 20 MG
PAROXETINE HCl

FOR DEPRESSION

PAXIL™ (brand of paroxetine hydrochloride)

See complete prescribing information in SmithKline Beecham Pharmaceuticals literature or *PDR*. The following is a brief summary.

INDICATIONS AND USAGE: *Paxil* is indicated for the treatment of depression.

CONTRAINDICATIONS: Concomitant use in patients taking monoamine oxidase inhibitors (MAOIs) is contraindicated. (See WARNINGS.)

WARNINGS: Interactions with MAOIs may occur. Given the fatal interactions reported with concomitant or immediately consecutive administration of MAOIs and other SSRIs, do not use *Paxil* in combination with a MAOI or within 2 weeks of discontinuing MAOI treatment. Allow at least 2 weeks after stopping *Paxil* before starting a MAOI.

PRECAUTIONS: As with all antidepressants, use *Paxil* cautiously in patients with a history of mania.

Use *Paxil* cautiously in patients with a history of seizures. Discontinue it in any patient who develops seizures.

The possibility of suicide attempt is inherent in depression and may persist until significant remission occurs. Close supervision of high-risk patients should accompany initial drug therapy. Write *Paxil* prescriptions for the smallest quantity of tablets consistent with good patient management in order to reduce the risk of overdose.

Reversible hyponatremia has been reported, mainly in elderly patients, patients taking diuretics or those who were otherwise volume depleted.

Clinical experience with *Paxil* in patients with concomitant systemic illness is limited. Use cautiously in patients with diseases or conditions that could affect metabolism or hemodynamic responses. Observe the usual cautions in cardiac patients. In patients with severe renal impairment (creatinine clearance <30 mL/min.) or severe hepatic impairment, a lower starting dose (10 mg) should be used.

Caution patients about operating hazardous machinery, including automobiles, until they are reasonably sure that *Paxil* therapy does not affect their ability to engage in such activities. Tell patients 1) to continue therapy as directed, 2) to inform physicians about other medications they are taking or plan to take; 3) to avoid alcohol while taking *Paxil*; 4) to notify their physicians if they become pregnant or intend to become pregnant during therapy, or if they're nursing.

Concomitant use of *Paxil* with tryptophan is not recommended.

Use cautiously with warfarin. When administering *Paxil* with cimetidine, dosage adjustment of *Paxil* after the 20 mg starting dose should be guided by clinical effect. When co-administering *Paxil* with phenobarbital or phenytoin, no initial *Paxil* dosage adjustment is needed, base subsequent changes on clinical effect. Concomitant use of *Paxil* with drugs metabolized by cytochrome $P_{450}IID_6$ (antidepressants such as nortriptyline, amitriptyline, imipramine, desipramine and fluoxetine, phenothiazines such as thioridazine, Type 1C antiarrhythmics such as propafenone, flecainide and encainide) or with drugs that inhibit this enzyme (e.g., quinidine) may require lower doses than usually prescribed for either *Paxil* or the other drug, approach concomitant use cautiously. Administration of *Paxil* with another tightly protein-bound drug may shift plasma concentrations, resulting in adverse effects from either drug. Concomitant use of *Paxil* and alcohol in depressed patients is not advised. Undertake concomitant use of *Paxil* and lithium or digoxin cautiously. If adverse effects are seen when co-administering *Paxil* with procyclidine, reduce the procyclidine dose.

In 2-year studies, a significantly greater number of male rats in the 20 mg/kg/day group developed reticulum cell sarcomas vs animals given doses of 1 or 5 mg/kg/day. There was also a significantly increased linear trend across dose groups for the occurrence of lymphoreticular tumors in male rats. Although there was a dose-related increase in the number of tumors in mice, there was no drug-related increase in the number of mice with tumors. The clinical significance of these findings is unknown. There is no evidence of mutagenicity with *Paxil*.

Serotonergic compounds are known to affect reproductive function in animals. Impaired reproductive function in rats (i.e., reduced pregnancy rate, increased pre- and post-implantation losses, decreased viability of pups) was found at *Paxil* doses 15 or more times the highest recommended human dose.

Pregnancy Category B. Reproduction studies performed in rats and rabbits at doses up to 50 and 6 times the maximum recommended human dose have revealed no evidence of teratogenic effects or of selective toxicity to the fetus. However, there are no adequate and well-controlled studies in pregnant women. *Paxil* should be used in pregnancy only if the benefits outweigh the risks. The effect of *Paxil* on labor and delivery in humans is unknown. Paroxetine is secreted in human milk; exercise caution when administering *Paxil* to a nursing woman.

Safety and effectiveness in children have not been established.

In worldwide *Paxil* clinical trials, 17% of *Paxil*-treated patients were ≥65 years of age. Pharmacokinetic studies revealed a decreased clearance in the elderly; however, there were no overall differences in the adverse event profile between older and younger patients.

ADVERSE REACTIONS: Incidence in Controlled Trials—*Commonly Observed Adverse Events in Controlled Clinical Trials:* The most commonly observed adverse events associated with the use of *Paxil* (incidence of 5% or greater and incidence for *Paxil* at least twice that for placebo): asthenia (15% vs. 6%), sweating (11% vs. 2%), nausea (26% vs. 9%), decreased appetite (6% vs. 2%), somnolence (23% vs. 9%), dizziness (13% vs. 6%), insomnia (13% vs. 6%), tremor (8% vs. 2%), nervousness (5% vs. 3%), ejaculatory disturbance (13% vs. 0%) and other male genital disorders (10% vs. 0%). Twenty-one percent (881/4,126) of *Paxil* patients in worldwide clinical trials discontinued treatment due to an adverse event. The most common events (≥1%) associated with discontinuation and considered to be drug related include: somnolence, insomnia, agitation, tremor, anxiety, nausea, diarrhea, dry mouth, vomiting, asthenia, abnormal ejaculation, sweating. The following adverse events occurred in 6-week placebo-controlled trials of similar design at a frequency of 1% or more:

Body as a Whole: headache, asthenia, abdominal pain, fever, chest pain, trauma, back pain. **Cardiovascular:** palpitation, vasodilation, postural hypotension. **Dermatologic:** sweating, rash. **Gastrointestinal:** nausea, dry mouth, constipation, diarrhea, decreased appetite, flatulence, vomiting, oropharynx disorder, dyspepsia, increased appetite. **Musculoskeletal:** myopathy, myalgia, myasthenia. **Nervous System:** somnolence, dizziness, insomnia, tremor, nervousness, anxiety, paresthesia, libido decreased, agitation, drugged feeling, myoclonus, CNS stimulation, confusion. **Respiration:** respiratory disorder, yawn, pharyngitis. **Special Senses:** blurred vision, taste perversion. **Urogenital System:** ejaculatory disturbance, other male genital disorders, urinary frequency, urination disorder, female genital disorders.

Studies show a clear dose dependency for some of the more common adverse events associated with *Paxil* use. There was evidence of adaptation to some adverse events with continued *Paxil* therapy (e.g., nausea and dizziness). Significant weight loss may be an undesirable result of *Paxil* treatment for some patients but, on average, patients in controlled trials had minimal (about 1 lb) loss. In placebo-controlled clinical trials, *Paxil*-treated patients exhibited abnormal values on liver function tests no more frequently than placebo-treated patients.

Other Events Observed During the Premarketing Evaluation of *Paxil*: During premarketing assessment, multiple doses of *Paxil* were administered to 4,126 patients, and the following adverse events were reported. Note: "frequent" = events occurring in at least 1/100 patients; "infrequent" = 1/100 to 1/1000 patients; "rare" = less than 1/1000 patients. Events are classified within body system categories and enumerated in order of decreasing frequency using the following definitions. It is important to emphasize that although the events occurred during *Paxil* treatment, they were not necessarily caused by it.

Body as a Whole: *frequent:* chills, malaise; *infrequent:* allergic reaction, carcinoma, face edema, moniliasis, neck pain; *rare:* abscess, adrenergic syndrome, cellulitis, neck rigidity, pelvic pain, peritonitis, ulcer. **Cardiovascular System:** *frequent:* hypertension, syncope, tachycardia; *infrequent:* bradycardia, conduction abnormalities, electrocardiogram abnormal, hypotension, migraine, peripheral vascular disorder; *rare:* angina pectoris, arrhythmia, atrial fibrillation, bundle branch block, cerebral ischemia, cerebrovascular accident, congestive heart failure, low cardiac output, myocardial infarct, myocardial ischemia, pallor, phlebitis, pulmonary embolus, supraventricular extrasystoles, thrombosis, varicose vein, vascular headache, ventricular extrasystoles. **Digestive System:** *infrequent:* bruxism, dysphagia, eructation, gastritis, glossitis, increased salivation, liver function tests abnormal, mouth ulceration, rectal hemorrhage; *rare:* aphthous stomatitis, bloody diarrhea, bulimia, colitis, duodenitis, esophagitis, fecal impactions, fecal incontinence, gastritis, gastroenteritis, gingivitis, hematemesis, hepatitis, ileus, jaundice, melena, peptic ulcer, salivary gland enlargement, stomach ulcer, stomatitis, tongue edema, tooth caries. **Endocrine System:** *rare:* diabetes mellitus, hyperthyroidism, hypothyroidism, thyroiditis. **Hemic and Lymphatic Systems:** *infrequent:* anemia, leukopenia, lymphadenopathy, purpura; *rare:* abnormal erythrocytes, eosinophilia, leukocytosis, lymphedema, abnormal lymphocytes, lymphocytosis, microcytic anemia, monocytosis, normocytic anemia. **Metabolic and Nutritional:** *frequent:* edema, weight gain, weight loss; *infrequent:* hyperglycemia, peripheral edema, thirst; *rare:* alkaline phosphatase increased, bilirubinemia, dehydration, gout, hypercholesteremia, hypocalcemia, hypoglycemia, hypokalemia, hyponatremia, SGOT increased, SGPT increased. **Musculoskeletal System:** *infrequent:* arthralgia, arthritis; *rare:* arthrosis, bursitis, myositis, osteoporosis, tetany. **Nervous System:** *frequent:* amnesia, CNS stimulation, concentration impaired, depression, emotional lability, vertigo; *infrequent:* abnormal thinking, akinesia, alcohol abuse, ataxia, convulsions, depersonalization, hallucinations, hyperkinesia, hypertonia, incoordination, lack of emotion, manic reaction, paranoid reaction; *rare:* abnormal electroencephalogram, abnormal gait, antisocial reaction, choreoathetosis, delirium, delusions, diplopia, drug dependence, dysarthria, dyskinesia, dystonia, euphoria, fasciculations, grand mal convulsion, hostility, hyperalgesia, hypokinesia, hysteria, libido increased, manic-depressive reaction, meningitis, myelitis, neuralgia, neuropathy, nystagmus, paralysis, psychosis, psychotic depression, reflexes increased, stupor, withdrawal syndrome. **Respiratory System:** *frequent:* cough increased, rhinitis; *infrequent:* asthma, bronchitis, dyspnea, epistaxis, hyperventilation, pneumonia, respiratory flu, sinusitis; *rare:* carcinoma of lung, hiccups, lung fibrosis, sputum increased. **Skin and Appendages:** *frequent:* pruritus; *infrequent:* acne, alopecia, dry skin, ecchymosis, eczema, furunculosis, urticaria; *rare:* angioedema, contact dermatitis, erythema nodosum, maculopapular rash, photosensitivity, skin discoloration, skin melanoma. **Special Senses:** *infrequent:* abnormality of accommodation, ear pain, eye pain, mydriasis, otitis media, taste loss, tinnitus; *rare:* amblyopia, cataract, conjunctivitis, corneal ulcer, exophthalmos, eye hemorrhage, glaucoma, hyperacusis, otitis externa, photophobia. **Urogenital System:** *infrequent:* abortion, amenorrhea, breast pain, cystitis, dysmenorrhea, dysuria, menorrhagia, nocturia, polyuria, urethritis, urinary incontinence, urinary retention, urinary urgency, vaginitis; *rare:* breast atrophy, breast carcinoma, breast neoplasm, female lactation, hematuria, kidney calculus, kidney function abnormal, kidney pain, mastitis, nephritis, oliguria, prostatic carcinoma, vaginal moniliasis.

Non-U.S. Postmarketing Reports

Voluntary reports of adverse events that have been received since market introduction and may have no causal relationship with *Paxil* include elevated liver function tests (the most severe case was a death due to liver necrosis, and one other case involving grossly elevated transaminases associated with severe liver dysfunction).

DRUG ABUSE AND DEPENDENCE: Controlled Substance Class: *Paxil* is not a controlled substance. Evaluate patients carefully for history of drug abuse and observe such patients closely for signs of *Paxil* misuse or abuse (e.g., development of tolerance, incrementations of dose, drug-seeking behavior).

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PROGRAM PROFILE

Center For Musculoskeletal Tumors

A CASE STUDY

A 35-year-old law student developed progressive pain in his hip. He eventually fell, sustaining a fracture through his femoral neck. At that time, a big tumor was detected in the proximal third of this femur, with the added complication of spillage into the hip joint. A biopsy confirmed an osteosarcoma, with no evidence of metastatic tumor. After three courses of chemotherapy, the patient underwent surgery.

This was a complicated case because of the tumor spillage. In order to achieve an adequate margin around the tumor, Dr. Menendez not only had to remove the proximal femur and surrounding musculature, but also the entire hip joint en bloc, including acetabulum, as well. Because the patient asked the team to reconstruct a leg that he could walk on and a hip he could move, surgeons opted against a fusion and instead performed a procedure that involved an allograft to reconstruct the acetabulum, and a custom endoprosthesis to replace the joint.

Following surgery, the patient underwent some follow-up chemotherapy. He had essentially 100 percent tumor necrosis, and an excellent response to chemotherapy. His allografts and junctions have since healed, and after a year he is ambulating with a cane — and continuing his pursuit of a law degree.

Malignant tumors of the musculoskeletal system, whether bone or soft tissue tumors, are extremely rare: only an estimated 4,000 new cases of osteogenic sarcoma, and 6,000 new cases of soft tissue sarcomas of the extremities, are diagnosed each year. Consequently, orthopaedic surgeons in private practice may see a malignant bone tumor perhaps once every 10 years.

In sharp contrast, Lawrence R. Menendez, M.D., associate professor of Orthopaedic Surgery at the University of Southern California School of Medicine and director of Orthopaedic Oncology at USC University Hospital, performs more than 200 procedures a year. This volume, supported by a multidisciplinary team of medical oncologists, musculoskeletal pathologists, vascular and plastic surgeons and radiation therapists, along with nursing, social and rehabilitative services at USC University Hospital, has allowed Dr. Menendez to develop and maintain an expertise in this specialized field.

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Bone Tumors

Benign and malignant bone tumors each present its own specific treatment challenges, making it imperative that an accurate diagnosis be established. Dr. Menendez treats the most common malignant bone tumor, osteogenic sarcoma, with biopsy and then he develops a comprehensive treatment strategy that may include staging studies, pre- and post-operative treatment with chemotherapy and/or radiation therapy, surgery and reconstruction, rehabilitation, and long-term follow-up to detect tumor recurrence. Reconstruction options include allografts, autologous bone grafts, prosthetic implants or a combination of these materials.

Soft Tissue Tumors

Soft tissue tumors that appear benign may actually be malignant, again requiring absolute accuracy of diagnosis. Oftentimes, large soft tissue resections will require extensive reconstructive surgery involving vascularized flaps to provide tissue coverage. At USC, Dr. Menendez has immediate access to the expertise of vascular surgeons, general surgeons and reconstructive surgeons to provide necessary treatment. As a result, he is prepared for any situation.

Close Contact With Referring Physicians

Follow-up is a vital aspect of the program. Dr. Menendez examines X-rays and exchanges notes with referring physicians, keeping all parties involved. He sends referring physicians a letter every time he sees their patients in follow-up, whether it is a month or five years later. Dr. Menendez follows patients who had malignancies every three months for the first two years, and then every six months. Regular check-ups are recommended for the life of the patient, although Dr. Menendez considers the patient cured if five years pass without a recurrence of metastatic disease.

Lawrence R. Menendez, M.D.:
At the forefront of orthopaedic oncology

About the Director

Lawrence R. Menendez, M.D., predicts that the future of musculoskeletal oncology will be centered within the major academic centers across the country, and believes USC is well-positioned to offer leadership in this complex field.

Born and raised in New Jersey, Dr. Menendez attended Middlebury College in Vermont, where he received his bachelor's degree in biology. He earned his medical degree from the New York University School of Medicine, completed a general surgery internship at Columbia Presbyterian Medical Center, and returned to New York University for his orthopaedic surgery residency. He also did an oncology fellowship at the University of Florida with William F. Enneking, M.D., one of the founders of orthopaedic oncology as a specialty.

From 1985 to 1989, Dr. Menendez served on the full-time USC faculty as assistant professor of Orthopaedic Surgery, and then became a part-time faculty member, moving his private practice to The Hospital of the Good Samaritan in Los Angeles. During this time, he continued to run the orthopaedic oncology service at Los Angeles County+USC Medical Center. In July 1992, he was recruited back to USC full time as associate professor.

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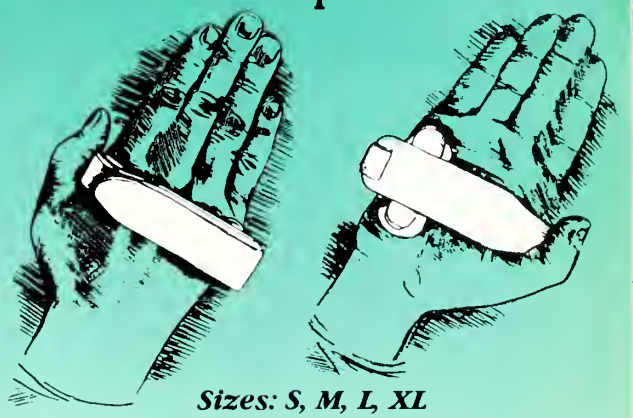

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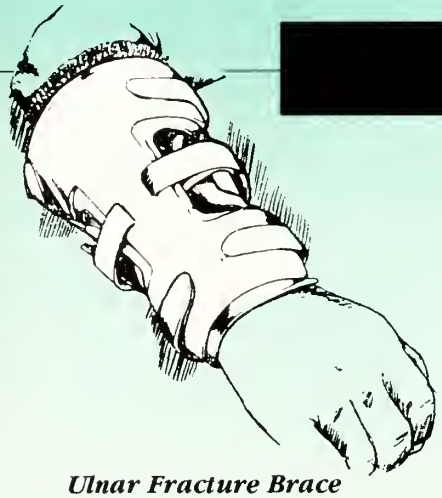

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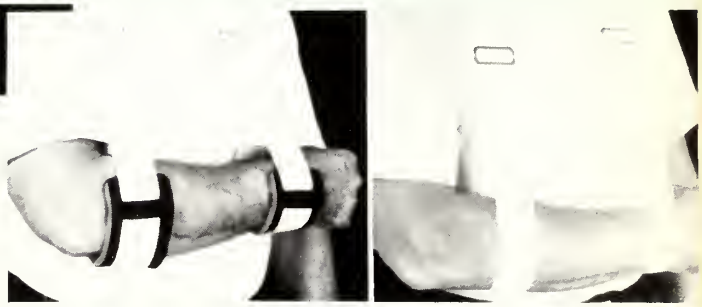

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ALLERGY/IMMUNOLOGY

September 30-October 2—**1st International Conference on Engineered Vaccines for Cancer and AIDS.** St Francis Memorial Hospital and Northern California Melanoma Center at Fairmont Hotel, San Francisco. Thurs-Sat. Contact: Cass Jones, 7916 Convoy Ct, San Diego 92111. (619) 565-9921.

ANESTHESIOLOGY

September 11-12—**Case Conference in Anesthesia.** California Society of Anesthesiology at Hyatt Hotel, Fisherman's Wharf, San Francisco. Sat-Sun. 9 hrs. $195. Contact: CSA, 1065 E Hillsdale Blvd, Ste 410, Foster City 94404. (800) 345-3691.

October 17-23—**Hawaiian Seminar on Clinical Anesthesia.** California Society of Anesthesiologists at Four Seasons Hotel, Wailea, Maui, Hawaii. Sun-Sat. 23 hrs. $425. Contact: CSA, 1065 E Hillsdale Blvd, Ste 410, Foster City 94404. (800) 345-3691.

November 12-14—**Anesthesiology Update: 1993.** UCD at Monterey Plaza. Fri-Sun. Contact: UCD.

November 19-20—**3rd Annual Pain Management.** UCD at Silverado Country Club, Napa. Fri-Sat. Contact: UCD.

January 16-22—**Hawaiian Seminar on Clinical Anesthesia.** California Society of Anesthesiologists at Westin Maui, Kaanapali Beach. Sun-Sat. 21 hrs. $425. Contact: CSA, 1065 E Hillsdale Blvd, Ste 410, Foster City 94404. (800) 345-3691.

January 28-30—**32nd Clinical Conference in Pediatric Anesthesiology.** Children's Hospital Los Angeles at Disneyland Hotel, Anaheim. Fri-Sun. 15 hrs. Contact: Children's Hospital, PO Box 54700, Los Angeles 90054. (213) 669-2262.

CARDIOLOGY

September 7-10—**Coronary Interventions: 1993.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Tues-Fri. 24 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, 403C, La Jolla 92037. (619) 554-8556.

October 1-3—**Coronary Interventions: 1993.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Fri-Sun. 14 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

October 14-16—**Cardiology Update: 1993.** UCSF at Quail Lodge Resort and Conference Center, Carmel. Thurs-Sat. 12 hrs. $445. Contact: UCSF.

CARDIOVASCULAR DISEASE

September 28-October 1—**47th Annual Fall Conference and Scientific Sessions of the Council for High Blood Pressure Research.** American Heart Association at Hyatt Regency, San Francisco. Tues-Fri. 21 hrs. Contact: AHA, 7272 Greenville Ave, Dallas, TX 75231. (214) 706-1511.

DERMATOLOGY

January 21-23—**Cutaneous Malignancies: 1994 Skin Cancer Update.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Fri-Sun. 17 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

January 21-23—**Practical Dermatology & Dermatologic Office Procedures for the Primary Care Physician.** UCSD at Hyatt Regency, La Jolla. Fri-Sun. 20 hrs. $495. Contact: Jacqueline Shiller, (619) 223-2997.

EMERGENCY MEDICINE

August 16-20—**Emergency Medicine Symposium II.** CMEA. Mon-Fri. 32 hrs. $495. Contact: Jacqueline Shiller, (619) 223-2997.

October 15-17—**Advances in Emergency Medicine.** UCSD at Hyatt Regency, La Jolla. Fri-Sun. 20 hrs. $450. Contact: UCSD.

October 18-22—**Emergency Medicine Symposium I.** UCSD at San Diego Hilton Beach and Tennis Resort. Mon-Fri. 32 hrs. $495. Contact: UCSD.

October 21-23—**Traumatic Brain Injury.** UCD at Hilton Hotel, Sacramento. Thurs-Sat. Contact: UCD.

November 8-12—**Emergency Medicine Symposium III.** UCSD at San Diego Hilton. Mon-Fri. 32 hrs. $495. Contact: UCSD.

December 5-10—**14th Annual Conference: Current Concepts in Emergency Care.** American College of Emergency Physicians Washington Chapter at Maui Intercontinental Resort, Maui, Hawaii. Sun-Fri. 20 hrs. Contact: Kailani World Travel, 4192 Meridian Ave, Box 9751, Bellingham, WA 98227. (800) 544-9269 or (206) 671-1800.

January 10-14—**Emergency Medicine Symposia I.** UCSD at La Jolla Marriott. Mon-Fri. 32 hrs. $495. Contact: UCSD.

January 22-29—**Update: Controversies in Emergency and Primary Care.** UCSD at The Royal Waikoloan, Kohala Coast, Hawaii. 1 wk. Contact: Edith Bookstein, PO Box 2586, La Jolla 92038. (619) 454-3212.

FAMILY PRACTICE/PRIMARY CARE

August 20-22—**Office Gynecology for the Primary Care Physician.** SDSU at Hyatt Islandia, San Diego. Fri-Sun. 20 hrs. $450. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

August 20-22—**Primary Care Medicine: A Practical Approach.** Scripps Clinic at Le Meridien San Diego. Fri-Sun. 16 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

September 11—**Primary Care Issues in Cardiac & Vascular Disease.** Alta Bates Medical Center at Claremont Resort, Berkeley. Sat. 7 hrs. $75. Contact: Mary Grim, (510) 204-1420.

October 6-8—**Primary Care Medicine: Principles and Practice.** UCSF at Nikko Hotel, San Francisco. Wed-Fri. 20 hrs. $485. Contact: UCSF.

October 6-9—**15th Semiannual Wound Management Workshop for Primary Care.** UCSD at San Diego Hilton. 17 hrs. $475. Contact: UCSD.

November 10-13—**North American Primary Care Research Group—Research Frontiers in Primary Care and Prevention.** UCSD at Hyatt Islandia on Mission Bay, San Diego. Wed-Sat. 23 hrs. $400. Contact: UCSD.

December 2-4—**Obstetrics and Gynecology Conference.** University of Nebraska at Bally's Las Vegas. Thurs-Sat. $275. Contact: University of Nebraska Medical Center, 600 S 42nd St, Omaha, NE 68198-5651. (402) 559-4152 or (800) 642-1095.

GERIATRICS

November 8-10—**Geriatrics Update: 1993.** Sharp Memorial Hospital at Loew's Coronado Bay Resort, San Diego. Mon-Wed. 20 hrs. $425. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

INFECTIOUS DISEASES

September 2-5—**HIV, AIDS, and Women.** UCSD at La Jolla Marriott. Thurs-Sun. 15 hrs. $200. Contact: UCSD.

November 5-7—**Advances in Infectious Disease.** Sharp Memorial Hospital at Loew's Coronado Bay Resort, San Diego. Fri-Sun. 20 hrs. $425. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

October 1-3—**Gastroenterology: Advances in Diagnosis and Management.** UCSF at Ana Hotel, San Francisco. Fri-Sun. 18 hrs. $430. Contact: UCSF.

October 14-16—**Recent Advances in Pulmonary and Critical Care Medicine.** UCSF at Ana Hotel, San Francisco. Thurs-Sat. 16 hrs. $415. Contact: UCSF.

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MEMORIAL/UCI CENTER FOR HEALTH EDUCATION

SEPTEMBER 1993

Chemosensitivity Assay
September 3, 1993
ORANGE, CALIFORNIA

Gastroenterology Update 1993
September 11, 1993
NEWPORT BEACH, CALIFORNIA

International Symposium on the Difficult Airway
September 17-19, 1993
NEWPORT BEACH, CALIFORNIA

OCTOBER 1993

16th Annual OB/GYN Review
October 18-19, 1993—Histapathalagy
October 20-23, 1993—OB/GYN
COSTA MESA, CALIFORNIA

Current Concepts in Clinical Medicine
October 25-28, 1993
KONA, HAWAII

NOVEMBER, 1993

6th Annual Transvaginal OB Ultrasound
November 5-7, 1993
ORANGE, CALIFORNIA

4th Annual Management of Diabetes
November 12-13, 1993
NEWPORT BEACH, CALIFORNIA

Ethics of Futile Care
November 13, 1993
LONG BEACH, CALIFORNIA

DECEMBER, 1993

Thoracoscopy for the Pulmonologist
December 3-4, 1993
LONG BEACH, CALIFORNIA

Incontinence/Upper Tract Disease for the Primary Care Physician
December 10-12, 1993
CHICAGO, ILLINOIS

1994

JANUARY, 1994

9th Annual Perinatal Symposium
January 12-16, 1994
BEAVER CREEK, COLORADO

Update in Urogynecology
January 16-20, 1994
GRAND CAYMAN, WEST INDIES

FEBRUARY, 1994

Cancer Imaging
February 11-12, 1994
NEWPORT BEACH, CALIFORNIA

The Neurologist and Back Pain
February 12-14, 1994
NEWPORT BEACH, CALIFORNIA

Incontinence/Upper Tract Disease for the Primary Care Physician
February 17-20, 1994
LOS ANGELES, CALIFORNIA

15th Roger K. Freeman Society Current Concepts in Obstetrics
February 19-26, 1994
ASPEN, COLORADO

MARCH, 1994

Oncology for the Gynecologist
March 7-11, 1994
LOCATION TBA

Advances in Urogynecology and Pelvic Surgery
March 10-12, 1994
PALM SPRINGS, CALIFORNIA

19th Annual Care of the Sick Newborn
March 23-25, 1994
LONG BEACH, CALIFORNIA

APRIL, 1994

3rd Annual OB/GYN Ultrasound
April 5-8, 1994
MAUI, HAWAII

Sweet Success Meeting
April 20-22, 1994
IRVINE, CALIFORNIA

MAY, 1994

5th Annual Philip J. DiSai Society Obstetric Gynecology Symposium
May 13, 1994
ORANGE, CALIFORNIA

UNIVERSITY OF CALIFORNIA, IRVINE

CENTER FOR HEALTH EDUCATION

LONG BEACH, CALIFORNIA

For further information contact the Center for Health Education ☎ Offices at (310) 933-3811.

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For further information, contact the office of Physician Education Services/CME at 616 S. Witmer St., Los Angeles, CA 90017 or call (213) 977-2335.

GOOD CARE
GOOD SAM

The Hospital of the Good Samaritan

Announces Its Fall 1993 CME Category I Symposium Program

Fall 1993

September 14, November 2
LA Cardiology Society Evening Forum
Heart Institute
David S. Cannom, M.D., course director

September 18
Advances in Cardiology 1993
Heart Institute
Robert A. Kloner, M.D., Ph.D., course director

September 30
Perinatal Evening with John C. Hauth, M.D.
Perinatal Center
"Prevention of Prematurity: Strategies for Intervention (HUAM)"
Robert Israel, M.D., course director

October 28
Heart Institute Visiting Professor Program
with Oscar B. Garfein, M.D.
Gregory L. Kay, M.D., course director

November 16
Advances in Epilepsy Evening
The Epilepsy and Brain Mapping Program
William W. Sutherling, M.D., course director

December 10-12
Advances in Clinical Neurosciences
Neurosciences Institute
Deane B. (Skip) Jacques, M.D.,
Robert W. Rand, Ph.D., M.D. and
Christopher M. Duma, M.D., course directors
Rancho Las Palmas Resort, Rancho Mirage

Coming in 1994

January 29
Arrhythmia Update 1994
Heart Institute
David S. Cannom, M.D. and Anil K. Bhandari, M.D., course directors

April 22
Stress Echo 1994: Practical Update
Heart Institute
Charles Pollick, M.D., course director

All CME activities are held in the hospital's Moseley-Salvatori Conference Center, unless otherwise indicated. Good Samaritan is a CMA-accredited provider of Category I CME hours.

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A source of strength in a world of resistance

CEFOBID® 1g/2g q12h

(cefoperazone sodium) IM/IV

Please see adjacent page for brief summary of prescribing information.

CEFOBID® (cefoperazone sodium) has maintained in vitro activity over time

- An excellent *in vitro* susceptibility profile against the most common nosocomial pathogens[1-3]

Pseudomonas aeruginosa[2,3]	
1985	1990
91.0%	93.1%
(n=388)	(n=15,439)

Staphylococcus aureus[2,3]	
1985	1990
92.0%	91.3%
(n=369)	(n=2,554)

From a retrospective, multicenter susceptibility data base; n=number of isolates; percent susceptible calculated with 95% confidence limits.

In vitro activity does not necessarily imply a correlation with *in vivo* results.

- An established record of clinical effectiveness in nosocomial pneumonia,* in complicated UTI,* and for approved indications in the febrile neutropenic patient*[4-8]
- No dosage adjustment required for the renally impaired
- Low sodium load
- Convenient, cost-effective q12h dosing

Contraindicated in patients with known allergy to the cephalosporin class of antibiotics

CEFOBID® 1g/2g q12h
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A force against resistance

*Due to susceptible strains of indicated organisms, such as *P aeruginosa*.

References: 1. Horan T, Culver D, Jarvis W, et al Pathogens causing nosocomial infections preliminary data from the National Nosocomial Infections Surveillance System *Antimicrobic Newsletter* 1988,5(9) 65-67 **2**. Data available on request from Roerig **3**. Jenkins SG Comparative susceptibility patterns of common clinical isolates to cefoperazone 1981 to 1987 *Am J Med* 1988,85(suppl 1A) 52-55 **4**. Mangi RJ, Greco T, Ryan J, Thorton G, Andriole VT Cefoperazone versus combination antibiotic therapy of hospital acquired pneumonia *Am J Med* 1988,84 68-74 **5**. Mangi RJ, Ryan J, Berenson C, et al Cefoperazone versus ceftazidime monotherapy of nosocomial pneumonia *Am J Med* 1988,85(suppl 1A) 44-48 **6**. Mangi R, Peccerillo K, Moleski RJ Treatment of nosocomial pneumonia Presented as an educational exhibit at the 47th Annual Meeting of the American Society of Hospital Pharmacists, June 3-7, 1990, Boston, Mass **7**. Cohen MS, Washton HE, Barranco SF Multicenter clinical trial of cefoperazone sodium in the United States *Am J Med* 1984,77 35-41 **8**. Kiehl A, Greenberg RN Treatment of febrile neutropenic patients evaluation of antibiotic regimens with or without vancomycin Presented at the 24th Annual ASHP Midyear Clinical Meeting, December 3-7, 1989, Atlanta Ga

Brief Summary

CEFOBID® (cefoperazone sodium) *For Intravenous or Intramuscular Use*

CONTRAINDICATIONS: CEFDBID (cefoperazone sodium) is contraindicated in patients with known allergy to the cephalosporin class of antibiotics **WARNINGS**. BEFDRE THERAPY WITH CEFDBID IS INSTITUTED, CAREFUL INDUIRY SHOULD BE MADE TD DETERMINE WHETHER THE PATIENT HAS HAD PREVIDUS HYPERSENSITIVITY REACTIONS TD CEPHALDSPDRINS, PENICILLINS DR DTHER DRUGS THIS PRDDUCT SHDULD BE GIVEN CAUTIDUSLY TD PENICILLIN-SENSITIVE PATIENTS ANTIBIDTICS SHDULD BE ADMINISTERED WITH CAUTIDN TD ANY PATIENT WHD HAS DEMDNSTRATED SDME FORM OF ALLERGY PARTICULARLY TD DRUGS SERIDUS ACUTE HYPERSENSITIVITY REACTIDNS MAY REQUIRE THE USE DF SUBCUTANEOUS EPINEPHRINE AND DTHER EMERGENCY MEASURES

PSEUDDMEMBRANDUS CDLITIS HAS BEEN REPDRTED WITH THE USE DF CEPHALDSPDRINS (AND DTHER BRDAD-SPECTRUM ANTIBIDTICS), THEREFDRE, IT IS IMPDRTANT TD CDNSIDER ITS DIAGNDSIS IN PATIENTS WHD DEVELDP DIARRHEA IN ASSDCIATIDN WITH ANTIBIDTIC USE **PRECAUTIONS**: Although transient elevations of the BUN and serum creatinine have been observed, CEFDBID alone does not appear to cause significant nephrotoxicity However concomitant administration of aminoglycosides and other cephalosporins has caused nephrotoxicity

CEFDBID is extensively excreted in bile The serum half-life of CEFDBID is increased 2-4 fold in patients with hepatic disease and/or biliary obstruction In general, total daily dosage above 4 g should not be necessary in such patients If higher dosages are used, serum concentrations should be monitored

Because renal excretion is not the main route of elimination of CEFDBID, patients with renal failure require no adjustment in dosage when usual doses are administered When high doses of CEFDBID are used, concentrations of drug in the serum should be monitored periodically If evidence of accumulation exists, dosage should be decreased accordingly

The half-life of CEFDBID is reduced slightly during hemodialysis Thus, dosing should be scheduled to follow a dialysis period In patients with both hepatic dysfunction and significant renal disease, CEFDBID dosage should not exceed 1-2 g daily without close monitoring of serum concentrations

As with other antibiotics, vitamin K deficiency has occurred rarely in patients treated with CEFDBID Those at risk include patients with a poor nutritional status, malabsorption states (e g , cystic fibrosis), alcoholism, and patients on prolonged hyperalimentation regimens (administered either intravenously or via a nasogastric tube) Prothrombin time should be monitored in these patients and exogenous vitamin K administered as indicated

A disulfiram-like reaction characterized by flushing, sweating, headache, and tachycardia has been reported when alcohol (beer, wine) was ingested within 72 hours after CEFDBID® (cefoperazone sodium) administration Patients should be cautioned about the ingestion of alcoholic beverages following the administration of CEFDBID A similar reaction has been reported with other cephalosporins

Prolonged use of CEFDBID may result in the overgrowth of nonsusceptible organisms Caretul observation of the patient is essential

CEFDBID should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis **Drug Laboratory Test Interactions**: A false-positive reaction for glucose in the urine may occur with Benedict's or Fehling's solution **Carcinogenesis, Mutagenesis, Impairment of Fertility**: The maximum duration of CEFDBID animal toxicity studies is six months In none of the *in vivo* or *in vitro* genetic toxicology studies did CEFDBID show any mutagenic potential at either the chromosomal or subchromosomal level CEFDBIO produced no impairment of fertility and had no effects on general reproductive performance or fetal development when administered subcutaneously at daily doses up to 500 to 1000 mg/kg prior to and during mating, and to pregnant female rats during gestation These doses are 10 to 20 times the estimated usual single clinical dose Cefoperazone had adverse effects on the testes of prepubertal rats at all doses tested Subcutaneous administration of 1000 mg/kg per day (approximately 16 times the average adult human dose) resulted in reduced germinal cell population and vacuolation of Sertoli cell cytoplasm The severity of lesions was dose dependent in the 100 to 1000 mg/kg per day range, the low dose caused a minor decrease in spermatocytes This effect has not been observed in adult rats Histologically the lesions were reversible at all but the highest dosage levels However, these studies did not evaluate subsequent development of reproductive function in the rats The relationship of these findings to humans is unknown **Usage in Pregnancy**. **Pregnancy Category B** Reproduction studies have been performed in mice, rats, and monkeys at doses up to 10 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to CEFDBIO There are, however, no adequate and well controlled studies in pregnant women Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed **Usage in Nursing Mothers**: Only low concentrations of CEFOBIO are excreted in human milk Although CEFDBIO passes poorly into breast milk of nursing mothers, caution should be exercised when CEFDBIO is administered to a nursing woman **Pediatric Use**. Safety and effectiveness in children have not been esfablished For information concerning testicular changes in prepubertal rats see Carcinogenesis, Mutagenesis, Impairment of Fertility **ADVERSE REACTIONS**: In clinical studies the following adverse effects were observed and were considered to be related to CEFDBID® (cefoperazone sodium) therapy or uncertain etiology **Hypersensitivity**: As with all cephalosporins, hypersensitivity manifested by skin reactions (1 patient in 45), drug fever (1 in 260), or a change in Coombs' test (1 in 60) has been reported These reactions are more likely to occur in patients with a history of allergies, particularly to penicillin **Hematology**: As with other beta-lactam antibiotics, reversible neutropenia may occur with prolonged administration Slight decreases in neutrophil count (1 patient in 50) have been reported Decreased hemoglobins (1 in 20) or hematocrits (1 in 20) have been reported, which is consistent with published literature on other cephalosporins Transient eosinophilia has occurred in 1 patient in 10 **Hepatic**: Of 1285 patients treated with cefoperazone in clinical trials one patient with a history of liver disease developed significantly elevated liver function enzymes during CEFDBID therapy Clinical signs and symptoms of nonspecific hepatitis accompanied these increases After CEFDBID therapy was discontinued, the patient's enzymes returned to pretreatment levels and the symptomatology resolved As with other antibiotics that achieve high bile levels, mild transient elevations of liver function enzymes have been observed in 5-10% of the patients receiving CEFDBID therapy The relevance of these findings, which were not accompanied by overt signs or symptoms of hepatic dysfunction, has not been established **Gastrointestinal**: Diarrhea or loose stools has been reported in 1 in 30 patients Most of these experiences have been mild or moderate in severity and self-limiting in nature In all cases, these symptoms responded to symptomatic therapy or ceased when cefoperazone therapy was stopped Nausea and vomiting have been reported rarely

Symptoms of pseudomembranous colitis can appear during or for several weeks subsequent to antibiotic therapy (see WARNINGS) **Renal Function Tests**: Transient elevations of the BUN (1 in 16) and serum creatinine (1 in 48) have been noted Local Reactions CEFDBID is well tolerated following intramuscular administration Occasionally, transient pain (1 in 140) may follow administration by this route When CEFDBID is administered by intravenous infusion some patients may develop phlebitis (1 in 120) at the infusion site

Pfizer Roerig

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Breast of chicken

3-oz. cooked serving of chicken breast

Best of pork

3-oz. cooked serving of pork tenderloin

Today's Pork: Compare it to chicken for a healthy surprise

You may not have considered pork to be a healthy choice for your patients on fat-modified diets. But today's fresh pork compares surprisingly well to chicken in total fat, saturated fat, cholesterol, and calories.[1,2*]

Compare pork with chicken[1,2*]

	Calories	Total Fat	Saturated Fatty Acids	Cholesterol
Chicken Breast, skinless	140	3.0 g	0.9 g	72 mg
Pork Tenderloin, trimmed	139	4.1 g	1.4 g	67 mg
Pork Top Loin Roast (boneless), trimmed	165	6.1 g	2.2 g	66 mg
Center Loin Chop, trimmed	172	6.9 g	2.5 g	70 mg
Chicken Thigh, skinless	178	9.2 g	2.6 g	81 mg

*Table refers to 3-oz, cooked servings.

New study: Pork is now 31% leaner

Pork is leaner today because of significant changes made in breeding and feeding techniques.[1] According to new 1992 official USDA data, fresh pork sold today contains an average of 31% less fat after cooking and trimming than the same pork cuts reported in 1983.[1]

Today's pork fits well within the dietary guidelines recommended by both the American Heart Association and the National Cholesterol Education Program. Here's some advice to help patients on low-fat diets enjoy the variety, extra taste, and versatility of pork:

- Choose the leanest cuts. Shop for cuts with "loin" in the name.
- Trim away any visible fat.
- Keep portions moderate (about 3 oz, cooked).
- Prepare by broiling or roasting, and avoid additional fat in preparation.

1. US Dept of Agriculture. *Composition of Foods: Pork Products*, 1992. Agricultural handbook 8-10.
2. US Dept of Agriculture. *Composition of Foods: Poultry Products*, 1979. Agricultural handbook 8-5.

Recommend

TODAY'S PORK

The Other White Meat®

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(Continued from Page 114)

INTERNAL MEDICINE

August 22-27—**New Advances in Internal Medicine.** UCD at Hyatt Regency, Monterey. Sun-Fri. 25 hrs. Contact: UCD.

OB/GYN

November 20—**Infertility Update VII.** Scripps Clinic and Research Foundation, La Jolla. Sat. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

December 2-4—**Obstetrics and Gynecology Conference.** University of Nebraska at Bally's Las Vegas. Thurs-Sat. $275. Contact: University of Nebraska Medical Center, 600 S 42nd St, Omaha, NE 68198-5651. (402) 559-4152 or (800) 642-1095.

OCCUPATIONAL/ENVIRONMENTAL

October 25-29—**Occupational and Environmental Medicine.** UCSF at Miyako Hotel, San Francisco. Mon-Fri. 40 hrs. $700. Contact: UCSF.

ONCOLOGY

October 23—**Biologic Agents of Solid Tumors.** UCD at Cancer Auditorium, Sacramento. Sat. Contact: UCD.

October 25-27—**17th Annual Cancer Symposium.** Scripps Memorial Hospital at Sheraton Harbor Island Hotel, San Diego. Mon-Wed. 20 hrs. $390. Contact: Cancer Symposium Conference Office, PO Box 16502, Irvine 92713-6338. (800) 321-6338.

November 4-5—**Growth Control, Signal Transduction and Oncogenesis.** UCLA at Beverly Hilton Hotel, Beverly Hills. Thurs-Sat. 12.75 hrs. $113-$150. Contact: UCLA Extension.

November 5-6—**American College of Surgeons: Cancer Management Course.** UCD at Cancer Center Auditorium, Sacramento. Fri-Sat. 13 hrs. $400. Contact: UCD.

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690. (415) 541-0900.

CPMC: California Pacific Medical Center
Contact: Continuing Education, California Pacific Medical Center, PO Box 7999, San Francisco 94120. (415) 923-3441.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Herbert M. Thomas, MD, MPH, Director of CME, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th St, Los Angeles 90059. (213) 603-3183.

LLU: Loma Linda University
Contact: James J. Couperus, MD, Associate Dean for Educational Affairs, Loma Linda University School of Medicine, Loma Linda 92350.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Medical School Office Building, Suite X-365, Stanford 94305-6114. (415) 723-5594.

UCD: University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, 2701 Stockton Blvd, Sacramento 95817. (916) 734-5390.

UCI: University of California, Irvine
Contact: Melvin I. Marks, MD, Director, Memorial/UCI Center for Health Education, Long Beach Memorial Medical Center, 2801 Atlantic Ave, PO Box 1428, Long Beach, California 90801-1428. (213) 595-3811.

UCLA: University of California, Los Angeles Extension
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, PO Box 24902, UCLA, Los Angeles 90024. (310) 825-8423.

UCSD: University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (619) 534-3940.

UCSF: University of California, San Francisco
Contact: Janet Johnson, Administrative Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 476-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 1975 Zonal Ave, KAM314, Los Angeles 90033. (800) 872-1119.

OPHTHALMOLOGY

September 10-12—**12th Annual Educational Conference: California Association of Ophthalmology.** California Association of Ophthalmology at Ana Hotel, San Francisco. Fri-Sun. 12.5 hrs. Contact: CAO, (415) 777-3937.

September 18—**General Medicine Update for Ophthalmologists.** UCD at Cancer Center Auditorium, Sacramento. Sat. Contact: UCD.

October 16—**Annual Ophthalmology Update: 1993.** UCD at Cancer Auditorium at Sacramento. Sat. Contact: UCD.

ORTHOPAEDICS

September 29-October 2—**6th Annual Comprehensive Foot and Ankle Course.** American Academy of Orthopaedic Surgeons at Sheraton Palace Hotel/Summit Health Education Center, San Francisco. Wed-Sat. Contact: AAOS, 6300 N River Rd, Rosemont, IL 60018-4262. (800) 346-2207.

October 18-20—**The Knee and Shoulder in Sports.** American College of Sports Medicine at Westin Maui, Kaanapali Beach, Maui, Hawaii. Mon-Wed. 13 hrs. $300. Contact: Stuart Zeman, MD, (800) 346-3277.

October 29-30—**Revision Total Hip in the 1990s.** American Academy of Orthopaedic Surgeons at US Grant Hotel, San Diego. Fri-Sat. Contact: AAOS, 6300 N River Rd, Rosemont, IL 60018-4262. (800) 346-2207.

November 5-9—**Fractures of the Pelvis and Acetabulum.** American Academy of Orthopaedic Surgeons at Marriott's Rancho Las Palmas Resort and Country Club Annenberg Center, Eisenhower Medical Center, Rancho Mirage. Fri-Tues. Contact: AAOS, 6300 N River Rd, Rosemont, IL 60018-4262. (800) 346-2207.

December 3-5—**Review and Update for Practicing Orthopaedic Surgeons.** American Academy of Orthopaedic Surgeons at Sheraton Palace Hotel, San Francisco. Fri-Sun. Contact: AAOS, 6300 N River Rd, Rosemont, IL 60018-4262. (800) 346-2207.

December 8-12—**American Back Society Meeting.** American Back Society at Hyatt Regency Embarcadero, San Francisco. Wed-Sun. Contact: ABS, 2647 E 14th St, Ste 401, Oakland 94601. (510) 536-9929.

OTOLARYNGOLOGY

November 4-6—**The San Francisco Otology, Neurotology, and Skull Base Surgery Update—1993.** UCSF at Ritz-Carlton Hotel, San Francisco. Thurs-Sat. 22 hrs. $395. Contact: UCSF.

PATHOLOGY

October 2—**33rd Annual Scientific Symposium on Kidney Disease.** National Kidney Foundation of Southern California at Stouffer Esmeralda Resort, Indian Wells. Sat. $125. Contact: Sylvie Tarro, (310) 641-8152.

October 25-29—**19th Annual Lukes Conference: Diagnostic Approaches to Lymphoproliferative Disorders.** Fri-Tues. 27 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

PEDIATRICS

August 23-25—**Pediatrics Update: 1993.** SDSU at Hyatt Islandia, San Diego. Mon-Wed. 20 hrs. $450. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

January 24-28—**San Diego Conference on Responding to Child Maltreatment.** Children's Hospital San Diego at Town and Country Hotel, San Diego. Mon-Fri. $390. Contact: Center for Child Protection, 8001 Frost St, San Diego 92123. (619) 395-4950.

PSYCHIATRY

September 18—**Beyond the Basics II.** San Francisco Academy of Hypnosis Education at Letterman Medical Center, San Francisco. Sat. $125. Contact: Jan Brooks, 615 27th Ave, San Francisco 94131. (415) 282-3399.

RADIOLOGY

October 3-6—**Current Concepts of Magnetic Resonance.** Stanford and Duke University at Ritz-Carlton Resort Hotel, Laguna Niguel. Sun-Wed. 22.75 hrs. $450-$550. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

(Continued on Page 128)

American Back Society
Cost Effective Back Care

December 1 - 4, 1993
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Earn 24 hours Category 1 CME Credit

How to Work with a Family Practitioner
California Back School 18 Years of Results
McKenzie Protocol
Aquatic Rehabilitation
San Francisco Spine CenterCreating
Therapy Based on Outcome
Somatic, Referred, & Radicular Pain
Managed Competition
Psychological Assessment
John Barnes' Myofascial Release
Structural Assessment
Dermatomes with Brain Mapping
Feldenkrais
Selective Nerve Root Blocks
Economical Treatment of Disc Disease
Osteometabolic Diseases
OSHA's Ergonomic Prevention Program
Intradiscal Proliferant Therapy
Abuse of Imaging
Spinal Deformities in the Adult
Advanced Pain Management
Testing / Exercise Training
The Lumbopelvic Ligaments
Spinal Imaging
Calcified Disk Herniations
Managed Competition
Abuse of Spinal Surgery
Family Practitioners Guide
Maximizing Reimbursement
Spinal Trauma • Spinal Orthoses
Lumbar Extension Exercises
Spinal Manipulation
Computerizing the Spine Center
Work Hardening
Arthroscopic Discectomy
Legislative Changes in Healthcare
Sacroiliac Dysfunction
Saint Mary's Spine Center
Diagnostic & Therapeutic Injections
Psychiatric Assessment
Electrodiagnosis
The Industrial Consultant
Tired Neck Syndrome
Family Pratitioner & Back Pain
Hysteria, Malingering, & Fraud
Non-Surgical Sciatic Pain
Medical & Legal Issues
Vocational Rehabilitation
Diagnosis of Thoracic Pain
Cervical Spine Pain
Functional Restoration
TMJ & Craniofascial Pain
The Role of Conditioning
Acupuncture
Osteopathic Medical Principles
Biofeedback Therapy
Disability Evaluation
Healthcare Reform

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ATTENTION
PHYSICIANS, MDs AND DOs
PhD AND MASTERS LEVEL PSYCHOLOGISTS
AND DIETITIANS

Have you read the newspaper headlines?
Commercial weight loss centers are closing down and filing bankruptcy nationwide. There must be a reason!
Obesity is a disease entity and should be treated by compassionate and knowledgeable physicians who can diagnose and treat this medical problem.

JUDGE THE FACTS:

- 34 million Americans need your help
- Physicians treat less than 1% of the obese population

LEARN HOW TO PROPERLY TREAT OBESITY by attending any one of the CME courses of the American Society of Bariatric Physicians (ASBP). For 43 years, the ASBP, an accredited provider of Category 1 CME, has been teaching physicians how to improve obese patients' lives.

Please send information on:

❒ Basic Bariatric Course, Nov 3-4, 1993, Sahara Hotel, Las Vegas, NV.
❒ Marketing Your Bariatric Practice, Nov 4, 1993, Sahara Hotel, Las Vegas, NV.
❒ 43rd Annual Obesity and Associated Conditions Symposium, Nov 5-7, 1993, Sahara Hotel, Las Vegas, NV.
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Discover The Elegance Of A Hybrid

At first glance, it's the ***beauty*** of a rose that catches the eye. The vibrant color. The delicately shaped petals. But study it more closely, and its ***elegance*** becomes apparent—a gentle blend of softness and strength.

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USE IN PREGNANCY: When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, Vaseretic® (Enalapril Maleate-Hydrochlorothiazide) should be discontinued as soon as possible. See WARNINGS, *Fetal/Neonatal Morbidity and Mortality.*

VASERETIC® 10-25 *Next*
Enalapril Maleate-Hydrochlorothiazide

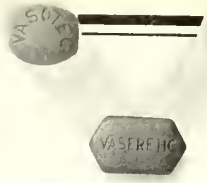
Dosage must be individualized; the fixed combination is not for initial therapy.

Evaluation of the hypertensive patient should always include assessment of renal function.

For a Brief Summary of Prescribing Information, see adjacent pages.

TABLETS
VASERETIC®
(ENALAPRIL MALEATE-HYDROCHLOROTHIAZIDE)

USE IN PREGNANCY: When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, VASERETIC® (Enalapril Maleate-Hydrochlorothiazide) should be discontinued as soon as possible. See WARNINGS, *Fetal/Neonatal Morbidity and Mortality.*



10 mg

25 mg

CONTRAINDICATIONS: VASERETIC is contraindicated in patients who are hypersensitive to any component of this product and in patients with a history of angioedema related to previous treatment with an angiotensin converting enzyme inhibitor. Because of the hydrochlorothiazide component, this product is contraindicated in patients with anuria or hypersensitivity to other sulfonamide-derived drugs.

WARNINGS: *General, Enalapril Maleate, Hypotension.* Excessive hypotension was rarely seen in uncomplicated hypertensive patients but is a possible consequence of enalapril use in severely salt/volume depleted persons such as those treated vigorously with diuretics or patients on dialysis.

Syncope has been reported in 1-3 percent of patients receiving VASERETIC. In patients receiving enalapril alone, the incidence of syncope is 0.5 percent. The overall incidence of syncope may be reduced by proper titration of the individual components. (See PRECAUTIONS, *Drug Interactions*, and ADVERSE REACTIONS.)

In patients with severe congestive heart failure, with or without associated renal insufficiency, excessive hypotension has been observed and may be associated with oliguria and/or progressive azotemia, and rarely with acute renal failure and/or death. Because of the potential fall in blood pressure in these patients, therapy should be started under very close medical supervision. Such patients should be followed closely for the first two weeks of treatment and whenever the dose of enalapril and/or diuretic is increased. Similar considerations may apply to patients with ischemic heart or cerebrovascular disease, in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident.

If hypotension occurs, the patient should be placed in the supine position and, if necessary, receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses, which usually can be given without difficulty once the blood pressure has increased after volume expansion.

Angioedema: Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported in patients treated with angiotensin converting enzyme inhibitors, including enalapril. In such cases VASERETIC should be promptly discontinued and appropriate therapy and monitoring should be provided until complete and sustained resolution of signs and symptoms has occurred. In instances where swelling has been confined to the face and lips the condition has generally resolved without treatment, although antihistamines have been useful in relieving symptoms. Angioedema associated with laryngeal edema may be fatal. **Where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, appropriate therapy, e.g., subcutaneous epinephrine solution 1:1000 (0.3 mL to 0.5 mL) and/or measures necessary to ensure a patent airway, should be promptly provided.** (See ADVERSE REACTIONS.)

Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor (see also CONTRAINDICATIONS).

Neutropenia/Agranulocytosis. Another angiotensin converting enzyme inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression, rarely in uncomplicated patients but more frequently in patients with renal impairment especially if they also have a collagen vascular disease. Available data from clinical trials of enalapril are insufficient to show that enalapril does not cause agranulocytosis at similar rates. Marketing experience has revealed several cases of neutropenia or agranulocytosis in which a causal relationship to enalapril cannot be excluded. Periodic monitoring of white blood cell counts in patients with collagen vascular disease and renal disease should be considered.

Hydrochlorothiazide. Thiazides should be used with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. Cumulative effects of the drug may develop in patients with impaired renal function.

Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.

Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma.

The possibility of exacerbation or activation of systemic lupus erythematosus has been reported.

Lithium generally should not be given with thiazides (see PRECAUTIONS, *Drug Interactions, Enalapril Maleate and Hydrochlorothiazide*).

Pregnancy: Enalapril-Hydrochlorothiazide: There was no teratogenicity in rats given up to 90 mg/kg/day of enalapril (150 times the maximum human dose) in combination with 10 mg/kg/day of hydrochlorothiazide (2 1/2 times the maximum human dose) or in mice given up to 30 mg/kg/day of enalapril (50 times the maximum human dose) in combination with 10 mg/kg/day of hydrochlorothiazide (2 1/2 times the maximum human dose). At these doses, fetotoxicity expressed as a decrease in average fetal weight occurred in both species. No fetotoxicity occurred at lower doses, 30/10 mg/kg/day of enalapril-hydrochlorothiazide in rats and 10/10 mg/kg/day of enalapril-hydrochlorothiazide in mice.

When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, VASERETIC should be discontinued as soon as possible (See *Enalapril Maleate, Fetal/Neonatal Morbidity and Mortality*, below.)

Enalapril Maleate, Fetal/Neonatal Morbidity and Mortality: ACE inhibitors can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature. When pregnancy is detected, ACE inhibitors should be discontinued as soon as possible.

The use of ACE inhibitors during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to the ACE-inhibitor exposure.

These adverse effects do not appear to have resulted from intrauterine ACE-inhibitor exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to ACE inhibitors only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should make every effort to discontinue the use of VASERETIC as soon as possible.

Rarely (probably less often than once in every thousand pregnancies), no alternative to ACE inhibitors will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intraamniotic environment.

If oligohydramnios is observed, VASERETIC should be discontinued unless it is considered lifesaving for the mother. Contraction stress testing (CST), a non-stress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of *in utero* exposure to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function. Enalapril, which crosses the placenta, has been removed from neonatal circulation by peritoneal dialysis with some clinical benefit, and theoretically may be removed by exchange transfusion, although there is no experience with the latter procedure.

No teratogenic effects of enalapril were seen in studies of pregnant rats and rabbits. On a mg/kg basis, the doses used were up to 333 times (in rats), and 50 times (in rabbits) the maximum recommended human dose.

Hydrochlorothiazide, Teratogenic Effects. Reproduction studies in the rabbit, the mouse and the rat at doses up to 100 mg/kg/day (50 times the human dose) showed no evidence of external abnormalities of the fetus due to hydrochlorothiazide. Hydrochlorothiazide given in a two-litter study in rats at doses of 4 - 5.6 mg/kg/day (approximately 1 - 2 times the usual daily human dose) did not impair fertility or produce birth abnormalities in the offspring. Thiazides cross the placental barrier and appear in cord blood.

Nonteratogenic Effects. These may include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult.

PRECAUTIONS: *General, Enalapril Maleate, Impaired Renal Function:* As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe congestive heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with angiotensin converting enzyme inhibitors, including enalapril, may be associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death.

In clinical studies in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine were observed in 20 percent of patients. These increases were almost always reversible upon discontinuation of enalapril and/or diuretic therapy. In such patients renal function should be monitored during the first few weeks of therapy.

Some patients with hypertension or heart failure with no apparent preexisting renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when enalapril has been given concomitantly with a diuretic. This is more likely to occur in patients with pre-existing renal impairment. Dosage reduction of enalapril and/or discontinuation of the diuretic may be required.

Evaluation of the hypertensive patient should always include assessment of renal function.

Hemodialysis Patients: Anaphylactoid reactions have been reported in patients dialyzed with high-flux membranes (e.g., AN 69*) and treated concomitantly with an ACE inhibitor. In these patients consideration should be given to using a different type of dialysis membrane or a different class of antihypertensive agent.

Hyperkalemia: Elevated serum potassium (greater than 5.7 mEq/L) was observed in approximately one percent of hypertensive patients in clinical trials treated with enalapril alone. In most cases these were isolated values which resolved despite continued therapy, although hyperkalemia was a cause of discontinuation of therapy in 0.28 percent of hypertensive patients. Hyperkalemia was less frequent (approximately 0.1 percent) in patients treated with enalapril plus hydrochlorothiazide. Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with enalapril. (See *Drug Interactions.*)

Cough: Cough has been reported with the use of ACE inhibitors. Characteristically, the cough is nonproductive, persistent and resolves after discontinuation of therapy. ACE inhibitor-induced cough should be considered as part of the differential diagnosis of cough.

Surgery/Anesthesia: In patients undergoing major surgery or during anesthesia with agents that produce hypotension, enalapril may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Hydrochlorothiazide: Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals. All patients receiving thiazide therapy should be observed for clinical signs of fluid or electrolyte imbalance: hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Warning signs or symptoms of fluid and electrolyte imbalance, irrespective of cause, include dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, confusion, seizures, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting.

Hypokalemia may develop, especially with brisk diuresis, when severe cirrhosis is present, or after prolonged therapy. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Hypokalemia may cause cardiac arrhythmia and may also sensitize or exaggerate the response of the heart to the toxic effects of digitalis (e.g., increased ventricular irritability). Because enalapril reduces the production of aldosterone, concomitant therapy with enalapril attenuates the diuretic-induced potassium loss (see *Drug Interactions, Agents Increasing Serum Potassium*).

Although any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease), chloride replacement may be required in the treatment of metabolic alkalosis.

Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction, rather than administration of salt except in rare instances when the hyponatremia is life-threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Hyperuricemia may occur or frank gout may be precipitated in certain patients receiving thiazide therapy.

In diabetic patients dosage adjustments of insulin or oral hypoglycemic agents may be required. Hyperglycemia may occur with thiazide diuretics. Thus latent diabetes mellitus may become manifest during thiazide therapy.

The antihypertensive effects of the drug may be enhanced in the postsympathectomy patient.

If progressive renal impairment becomes evident consider withholding or discontinuing diuretic therapy.

Thiazides have been shown to increase the urinary excretion of magnesium; this may result in hypomagnesemia.

Thiazides may decrease urinary calcium excretion. Thiazides may cause intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

Increases in cholesterol and triglyceride levels may be associated with thiazide diuretic therapy.

Information for Patients, Angioedema. Angioedema, including laryngeal edema, may occur especially following the first dose of enalapril. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, extremities, eyes, lips, tongue, difficulty in swallowing or breathing) and to take no more drug until they have consulted with the prescribing physician.

Hypotension: Patients should be cautioned to report lightheadedness especially during the first few days of therapy. If actual syncope occurs, the patients should be told to discontinue the drug until they have consulted with the prescribing physician.

All patients should be cautioned that excessive perspiration and dehydration may lead to an excessive fall in blood pressure because of reduction in fluid volume. Other causes of volume depletion such as vomiting or diarrhea may also lead to a fall in blood pressure; patients should be advised to consult with the physician.

Hyperkalemia: Patients should be told not to use salt substitutes containing potassium without consulting their physician.

Neutropenia: Patients should be told to report promptly any indication of infection (e.g., sore throat, fever) which may be a sign of neutropenia.

Pregnancy: Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to ACE inhibitors, and they should also be told that these consequences do not appear to have resulted from intrauterine ACE-inhibitor exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.

NOTE: As with many other drugs, certain advice to patients being treated with VASERETIC is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Drug Interactions: Enalapril Maleate; Hypotension—Patients on Diuretic Therapy: Patients on diuretics and especially those in whom diuretic therapy was recently instituted, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with enalapril. The possibility of hypotensive effects with enalapril can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with enalapril. If it is necessary to continue the diuretic, provide medical supervision for at least two hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS.)

Agents Causing Renin Release: The antihypertensive effect of enalapril is augmented by antihypertensive agents that cause renin release (e.g., diuretics).

Other Cardiovascular Agents: Enalapril has been used concomitantly with beta adrenergic-blocking agents, methyldopa, nitrates, calcium-blocking agents, hydralazine and prazosin without evidence of clinically significant adverse interactions.

Agents Increasing Serum Potassium. Enalapril attenuates diuretic-induced potassium loss. Potassium-sparing diuretics (e.g., spironolactone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium. Therefore, if concomitant use of these agents is indicated because of demonstrated hypokalemia they should be used with caution and with frequent monitoring of serum potassium.

Lithium: Lithium toxicity has been reported in patients receiving lithium concomitantly with drugs which cause elimination of sodium, including ACE inhibitors. A few cases of lithium toxicity have been reported in patients receiving concomitant enalapril and lithium and were reversible upon discontinuation of both drugs. It is recommended that serum lithium levels be monitored frequently if enalapril is administered concomitantly with lithium.

Hydrochlorothiazide: When administered concurrently the following drugs may interact with thiazide diuretics:

Alcohol, barbiturates, or narcotics—potentiation of orthostatic hypotension may occur.

Antidiabetic drugs (oral agents and insulin)—dosage adjustment of the antidiabetic drug may be required.

Other antihypertensive drugs—additive effect or potentiation.

Cholestyramine and colestipol resins—Cholestyramine and colestipol resins bind the hydrochlorothiazide and reduce its absorption from the gastrointestinal tract by up to 85 and 43 percent, respectively. Thiazides may be administered two to four hours before the resin when the two drugs are used concomitantly.

Corticosteroids, ACTH—intensified electrolyte depletion, particularly hypokalemia.

Pressor amines (e.g., norepinephrine)—possible decreased response to pressor amines but not sufficient to preclude their use.

Skeletal muscle relaxants, nondepolarizing (e.g., tubocurarine)—possible increased responsiveness to the muscle relaxant.

Lithium—should not generally be given with diuretics. Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity. Refer to the package insert for lithium preparations before use of such preparations with VASERETIC.

Non-steroidal Anti-inflammatory Drugs—In some patients, the administration of a non-steroidal anti-inflammatory agent can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing and thiazide diuretics. Therefore, when VASERETIC and non-steroidal anti-inflammatory agents are used concomitantly, the patient should be observed closely to determine if the desired effect of the diuretic is obtained.

Carcinogenesis, Mutagenesis, Impairment of Fertility. Enalapril in combination with hydrochlorothiazide was not mutagenic in the Ames microbial mutagen test with or without metabolic activation. Enalapril-hydrochlorothiazide did not produce DNA single strand breaks in an *in vitro* alkaline elution assay in rat hepatocytes or chromosomal aberrations in an *in vivo* mouse

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bone marrow assay.

Enalapril Maleate: There was no evidence of a tumorigenic effect when enalapril was administered for 106 weeks to rats at doses up to 90 mg/kg/day (150 times* the maximum daily human dose). Enalapril has also been administered for 94 weeks to male and female mice at doses up to 90 and 180 mg/kg/day, respectively, (150 and 300 times* the maximum daily dose for humans) and showed no evidence of carcinogenicity.

Neither enalapril maleate nor the active diacid was mutagenic in the Ames microbial mutagen test with or without metabolic activation. Enalapril was also negative in the following genotoxicity studies: rec-assay, reverse mutation assay with *E. coli*, sister chromatid exchange with cultured mammalian cells, and the micronucleus test with mice, as well as in an *in vivo* cytogenic study using mouse bone marrow.

There were no adverse effects on reproductive performance in male and female rats treated with 10 to 90 mg/kg/day of enalapril.

Hydrochlorothiazide: Two-year feeding studies in mice and rats conducted under the auspices of the National Toxicology Program (NTP) uncovered no evidence of a carcinogenic potential of hydrochlorothiazide in female mice (at doses of up to approximately 600 mg/kg/day) or in male and female rats (at doses of up to approximately 100 mg/kg/day). The NTP, however, found equivocal evidence for hepatocarcinogenicity in male mice.

Hydrochlorothiazide was not genotoxic *in vitro* in the Ames mutagenicity assay of *Salmonella typhimurium* strains TA 98, TA 100, TA 1535, TA 1537, and TA 1538 and in the Chinese Hamster Ovary (CHO) test for chromosomal aberrations, or *in vivo* in assays using mouse germinal cell chromosomes, Chinese hamster bone marrow chromosomes, and the *Drosophila* sex-linked recessive lethal trait gene. Positive test results were obtained only in the *in vitro* CHO Sister Chromatid Exchange (clastogenicity) and in the Mouse Lymphoma Cell (mutagenicity) assays, using concentrations of hydrochlorothiazide from 43 to 1300 µg/mL, and in the *Aspergillus nidulans* non-disjunction assay at an unspecified concentration.

Hydrochlorothiazide had no adverse effects on the fertility of mice and rats of either sex in studies wherein these species were exposed, via their diet, to doses of up to 100 and 4 mg/kg, respectively, prior to conception and throughout gestation.

Pregnancy: Pregnancy Categories C (first trimester) *and D* (second and third trimesters). See WARNINGS, *Pregnancy, Enalapril Maleate, Fetal/Neonatal Morbidity and Mortality*

Nursing Mothers: Enalapril and enalaprilat are detected in human milk in trace amounts. Thiazides do appear in human milk. Because of the potential for serious reactions in nursing infants from either drug, a decision should be made whether to discontinue nursing or to discontinue VASERETIC, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: VASERETIC has been evaluated for safety in more than 1500 patients, including over 300 patients treated for one year or more. In clinical trials with VASERETIC no adverse experiences peculiar to this combination drug have been observed. Adverse experiences that have occurred, have been limited to those that have been previously reported with enalapril or hydrochlorothiazide.

The most frequent clinical adverse experiences in controlled trials were: dizziness (8.6 percent), headache (5.5 percent), fatigue (3.9 percent) and cough (3.5 percent). Adverse experiences occurring in greater than two percent of patients treated with VASERETIC in controlled clinical trials were: muscle cramps (2.7 percent), nausea (2.5 percent), asthenia (2.4 percent), orthostatic effects (2.3 percent), impotence (2.2 percent), and diarrhea (2.1 percent).

Clinical adverse experiences occurring in 0.5 to 2.0 percent of patients in controlled trials included: *Body As A Whole:* Syncope, chest pain, abdominal pain; *Cardiovascular:* Orthostatic hypotension, palpitation, tachycardia; *Digestive:* Vomiting, dyspepsia, constipation, flatulence, dry mouth; *Nervous/Psychiatric:* Insomnia, nervousness, paresthesia, somnolence, vertigo; *Skin:* Pruritus, rash, *Other:* Dyspnea, gout, back pain, arthralgia, diaphoresis, decreased libido, tinnitus, urinary tract infection.

Angioedema: Angioedema has been reported in patients receiving VASERETIC (0.6 percent). Angioedema associated with laryngeal edema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis and/or larynx occurs, treatment with VASERETIC should be discontinued and appropriate therapy instituted immediately. (See WARNINGS.)

Hypotension: In clinical trials, adverse effects relating to hypotension occurred as follows: hypotension (0.9 percent), orthostatic hypotension (1.5 percent), other orthostatic effects (2.3 percent). In addition syncope occurred in 1.3 percent of patients. (See WARNINGS.)

Cough: See PRECAUTIONS, *Cough*

Clinical Laboratory Test Findings, Serum Electrolytes. See PRECAUTIONS

Creatinine, Blood Urea Nitrogen: In controlled clinical trials minor increases in blood urea nitrogen and serum creatinine, reversible upon discontinuation of therapy, were observed in about 0.6 percent of patients with essential hypertension treated with VASERETIC. More marked increases have been reported in other enalapril experience. Increases are more likely to occur in patients with renal artery stenosis. (See PRECAUTIONS.)

Serum Uric Acid, Glucose, Magnesium, and Calcium: See PRECAUTIONS

Hemoglobin and Hematocrit: Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.3 g percent and 1.0 vol percent, respectively) occur frequently in hypertensive patients treated with VASERETIC but are rarely of clinical importance unless another cause of anemia coexists. In clinical trials, less than 0.1 percent of patients discontinued therapy due to anemia.

Liver Function Tests: Rarely, elevations of liver enzymes and/or serum bilirubin have occurred.

Other adverse reactions that have been reported with the individual components are listed below and, within each category, are in order of decreasing severity.

Enalapril Maleate—Enalapril has been evaluated for safety in more than 10,000 patients. In clinical trials adverse reactions which occurred with enalapril were also seen with VASERETIC. However, since enalapril has been marketed, the following adverse reactions have been reported: *Body As A Whole:* Anaphylactoid reactions (see PRECAUTIONS, *Hemodialysis Patients*); *Cardiovascular:* Cardiac arrest; myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high risk patients (see WARNINGS, *Hypotension*); pulmonary embolism and infarction, pulmonary edema; rhythm disturbances including atrial tachycardia and bradycardia, atrial fibrillation; hypotension; angina pectoris; *Digestive:* Ileus, pancreatitis, hepatic failure, hepatitis (hepatocellular [proven on rechallenge] or cholestatic jaundice), melena, anorexia, glossitis, stomatitis, dry mouth; *Hematologic:* Rare cases of neutropenia, thrombocytopenia and bone marrow depression, a few cases of hemolysis in patients with G-6-PD deficiency have been reported in which a causal relationship to enalapril cannot be excluded; *Nervous System/Psychiatric:* Depression, confusion, ataxia, peripheral neuropathy (e.g., paresthesia, dysesthesia); *Urogenital:* Renal failure, oliguria, renal dysfunction (see PRECAUTIONS), flank pain, gynecomastia; *Respiratory:* Pulmonary infiltrates, bronchospasm, pneumonia, bronchitis, rhinorrhea, sore throat and hoarseness, asthma, upper respiratory infection; *Skin:* Exfoliative dermatitis, toxic epidermal necrolysis, Stevens-Johnson syndrome, herpes zoster, erythema multiforme, urticaria, alopecia, flushing, photosensitivity, *Special Senses:* Blurred vision, taste alteration, anosmia, conjunctivitis, dry eyes, tearing.

Miscellaneous: A symptom complex has been reported which may include a positive ANA, an elevated erythrocyte sedimentation rate, arthralgia/arthritis, myalgia, fever, serositis, vasculitis, leukocytosis, eosinophilia, photosensitivity, rash and other dermatologic manifestations.

Fetal/Neonatal Morbidity and Mortality. See WARNINGS, *Pregnancy, Enalapril Maleate, Fetal/Neonatal Morbidity and Mortality.*

Hydrochlorothiazide—Body as a Whole: Weakness; *Digestive:* Pancreatitis, jaundice (intrahepatic cholestatic jaundice), sialadenitis, cramping, gastric irritation, anorexia; *Hematologic:* Aplastic anemia, agranulocytosis, leukopenia, hemolytic anemia, thrombocytopenia; *Hypersensitivity:* Purpura, photosensitivity, urticaria, necrotizing angiitis (vasculitis and cutaneous vasculitis), fever, respiratory distress including pneumonitis and pulmonary edema, anaphylactic reactions; *Musculoskeletal:* Muscle spasm; *Nervous System/Psychiatric:* Restlessness; *Renal:* Renal failure, renal dysfunction, interstitial nephritis (see WARNINGS); *Skin:* Erythema multiforme including Stevens-Johnson syndrome, exfoliative dermatitis including toxic epidermal necrolysis, alopecia; *Special Senses:* Transient blurred vision, xanthopsia.

* Based on patient weight of 50 kg.

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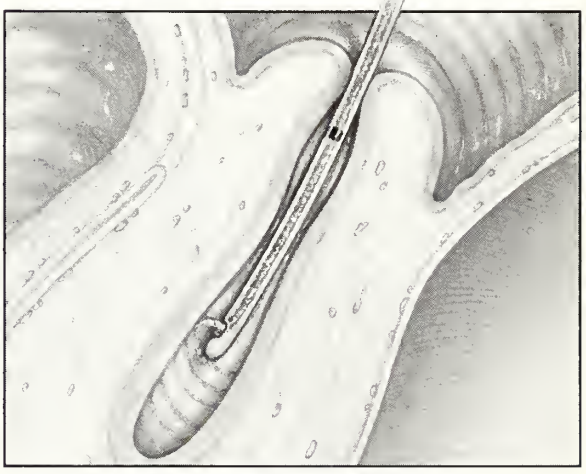

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In Memoriam

California Medical Association

ANDERSON, MICHAEL D., Placentia. Died Apr 8, 1993, aged 51. Graduate of Loma Linda University School of Medicine, 1967. Licensed in California in 1972. Dr Anderson was a member of the Orange County Medical Association.

APPLE, VICTOR H., Sacramento. Died Oct 12, 1992, aged 74. Graduate of University of Michigan Medical School, Ann Arbor, 1948. Licensed in California in 1954. Dr Apple was a member of the Sacramento-El Dorado Medical Society.

ARMSTRONG, WAYNE E., Portland. Died Mar 20, 1993, aged 63. Graduate of University of Michigan Medical School, Ann Arbor, 1954. Licensed in California in 1955. Dr Armstrong was a member of the Orange County Medical Association.

BEARDSLEY, LLOYD C., Jr, Arroyo Grande. Died Apr 16, 1993, aged 74. Graduate of University of Southern California, Los Angeles, 1944. Licensed in California in 1944. Dr Beardsley was a member of the Los Angeles County Medical Association.

BERNATH, GERALD D., Laguna Hills. Died May 1993, aged 87. Graduate of Wayne State University, 1929. Licensed in California in 1939. Dr Bernath was a member of the Orange County Medical Association.

BLUMENFELD, CHARLES M., Sacramento. Died Mar 15, 1993, aged 88. Graduate of University of Minnesota Medical School, Minneapolis, 1934. Licensed in California in 1945. Dr Blumenfeld was a member of the Sacramento-El Dorado Medical Society.

BOM, ROBERT HOLLOWAY, Rialto. Died May 5, 1993, aged 65. Graduate of Loma Linda University School of Medicine, Loma Linda, California, 1956. Licensed in California in 1966. Dr Bom was a member of the San Bernardino County Medical Society.

BUTLER, HARRY T., Napa. Died Apr 24, 1993, aged 79. Graduate of University of Oregon Medical School, Portland, 1943. Licensed in California in 1951. Dr Butler was a member of the Napa County Medical Society.

DEVNICH, HENRY E., Livermore. Died Dec 15, 1992, aged 82. Graduate of University of Nebraska College of Medicine, Omaha, 1945. Licensed in California in 1946. Dr Devnich was a member of the Alameda-Contra Costa Medical Association.

HAWKINS, G. WILLIAM, Orange. Died Mar 29, 1993, aged 75. Graduate of Stanford University School of Medicine, Stanford, California, 1944. Licensed in California in 1944. Dr Hawkins was a member of the Orange County Medical Association.

JAGATIC, JURAJ, Visalia. Died May 17, 1993, aged 66. Graduate of Med Fak, Sveucilista U Zabrebu, Zabreb, Yugoslavia, 1950. Licensed in California in 1971. Dr Jagatic was a member of the Tulare County Medical Society.

LEE, LAWRENCE Y., Tustin. Died Apr 24, 1993, aged 59. Graduate of University of California College of Medicine, Irvine, 1962. Licensed in California in 1963. Dr Lee was a member of the Orange County Medical Association.

LO PINTO, ANDREW F., San Diego. Died Apr 1993, aged 76. Graduate of University of Southern California School of Medicine, 1943. Licensed in California in 1943. Dr Lo Pinto was a member of the San Diego County Medical Society.

MCKEE, JOHN S., Jr, San Diego. Died Apr 10, 1993, aged 73. Graduate of Northwestern University School of Medicine, Chicago, Illinois, 1944. Licensed in California in 1955. Dr McKee was a member of the San Diego County Medical Society.

MOLONEY, SEAN, Sr, Daly City. Died Apr 20, 1993, aged 74. Graduate of National University of Ireland, 1948. Licensed in California in 1949. Dr Moloney was a member of the San Francisco Medical Society.

MORRIS, JAMES M., Jr, San Francisco. Died Mar 7, 1993, aged 59. Graduate of Stanford University School of Medicine, Stanford, California, 1958. Licensed in California in 1959. Dr Morris was a member of the San Francisco Medical Society.

OLSON, RAYMOND N., Davis. Died Sep 1992, aged 78. Graduate of Stanford University School of Medicine, Stanford, California, 1942. Licensed in California in 1942. Dr Olson was a member of the Yolo County Medical Society.

ROOT, GROSVENOR T., Oakland. Died Mar 3, 1993, aged 80. Graduate of University of Michigan Medical School, Ann Arbor, 1937. Dr Root was a member of the Alameda-Contra Costa Medical Association.

ROVNO, HERBERT, Santa Clara. Died Jun 1993, aged 98. Graduate of University of Pennsylvania School of Medicine, Philadelphia, 1925. Dr Rovno was a member of the Santa Clara County Medical Association.

SANDERSON, BRUCE A., San Diego. Died Nov 24, 1992, aged 77. Graduate of Loma Linda University School of Medicine, Loma Linda, California, 1945. Licensed in California in 1946. Dr Sanderson was a member of the San Diego County Medical Society.

SCHNITZER, HAROLD, Redlands. Died May 11, 1993, aged 71. Graduate of State University of New York Downstate College of Medicine, Brooklyn, 1953. Licensed in California in 1957. Dr Schnitzer was a member of the San Bernardino County Medical Society.

SWEARENGIN, PHARRIS V., Sacramento. Died Apr 16, 1993, aged 84. Graduate of University of California College of Medicine, Irvine, 1962. Licensed in California in 1975. Dr Swearengin was a member of the Sacramento-El Dorado Medical Society.

SYLVESTER, JAMES A., Fremont. Died May 1, 1993, aged 72. Graduate of University of Rochester School of Medicine, Rochester, New York, 1948. Licensed in California in 1951. Dr Sylvester was a member of the Alameda-Contra Costa Medical Association.

WERBEL, ERNEST W., San Luis Obispo. Died Apr 22, 1993, aged 84. Graduate of University of Illinois College of Medicine, Chicago, 1934. Licensed in California in 1947. Dr Werbel was a member of the San Luis Obispo County Medical Society.

ZAUGG, DAVID J., Walnut Creek. Died Apr 24, 1993, aged 84. Graduate of Case Western Reserve University School of Medicine, Cleveland, Ohio, 1934. Licensed in California in 1963. Dr Zaugg was a member of the Orange County Medical Association.

New Mexico Medical Society

ADLER, ELEANOR L., Albuquerque. Died Apr 11, 1993, aged 85. Graduate of Baylor Medical School, Houston, Texas, 1933. Licensed in New Mexico in 1946. Dr Adler was a member of the Greater Albuquerque Medical Association.

LOREE, HARRY E., Clovis. Died Apr 27, 1993, aged 71. Graduate of New York Medical College, 1946. Licensed in New Mexico in 1954. Dr Loree was a member of the Currey-Debaca-Roosevelt County Medical Society.

MERLE S. SCHERR, MD, of Scottsdale, Arizona, a member of our Editorial Board since 1986, died on July 6, 1993. We will miss his advice and counsel.

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References:

1. A. Morales et al., New England Journal of Medicine: 1221. November 12, 1981.
2. Goodman, Gilman — The Pharmacological basis of Therapeutics 6th ed., p. 176-188. McMillan December Rev. 1/85.
3. Weekly Urological Clinical Letter, 27:2, July 4, 1983.
4. A. Morales et al., The Journal of Urology 128: 45-47, 1982.

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(Continued from Page 120)

October 18-20—**Radiology for the Non-Radiologist.** UCSD at Hyatt Regency, San Diego. Mon-Wed. 20 hrs. $450. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

October 18-22—**Women's Imaging: An Update on Women's Health Issues.** Western Pennsylvania Hospital and University of Alabama at Birmingham at Ritz-Carlton Hotel, Laguna Niguel. Mon-Fri. 20 hrs. $525. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

October 23-24—**MRI of the Musculoskeletal System.** UCSD at Hotel del Coronado, San Diego. Sat-Sun. 9 hrs. $275. Contact: UCSD.

October 25-29—**18th Annual San Diego Postgraduate Radiology Course.** UCSD at Hotel del Coronado, San Diego. Mon-Fri. 25 hrs. $595. Contact: UCSD.

October 29-31—**Annual Interventional Radiology Course.** UCSD at Hotel del Coronado, San Diego. Fri-Sun. 16 hrs. $375. Contact: UCSD.

November 12-14—**Advanced Seminars in Diagnostic Imaging.** UCSD at Ritz-Carlton, Laguna Niguel. Fri-Sun. 20 hrs. $500. Contact: UCSD.

January 17-19—**Neuroradiology Update.** Stanford University Medical Center at Ritz-Carlton, Laguna Niguel. Mon-Wed. 17.5 hrs. $450. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

January 20-23—**Breast Imaging Update.** Stanford University Medical Center at Ritz-Carlton Hotel, Laguna Niguel. Thurs-Sun. 16 hrs. $450. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

RISK MANAGEMENT

September 27-28—**High Risk Emergency Medicine: Preventing Malpractice.** CAL/ACEP at Las Vegas, Nevada. Mon-Tues. 15 hrs. $345-$495. Contact: Kathy Hester, (800) 451-7475.

VASCULAR DISEASE

October 4-8—**A Comprehensive Review of What's New in Vascular Surgery.** UCLA at Miramar Sheraton Hotel, Santa Monica. Mon-Fri. 34 hrs. $487-$650. Contact: UCLA Extension.

GENERAL/MULTIDISCIPLINARY

October 14-17—**Women in Medicine.** UCSD at San Diego Hilton. Thurs-Sun. 15 hrs. $300. Contact: UCSD.

October 16—**12th Annual Sharrer Symposium: Change and Stress in Medicine—The Modern Physician.** Kaweah Delta District Hospital at Radisson Hotel, Visalia. Sat. 4 hrs. Contact: Susan Delgado, Continuing Education, (209) 625-7308.

October 27-31—**CME/Golf Meeting.** Nevada Academy of Family Physicians Las Vegas Chapter at Rio Hotel, Las Vegas. Wed-Sun. 23 hrs. $75. Contact: Barbara Bolling, PO Box 27713, Las Vegas, NV 89126-1713. (702) 647-0117.

HOME STUDY/SELF ASSESSMENT

Audio-Digest Foundation. California Medical Association. Contact: Audio-Digest Foundation, 1577 E Chevy Chase, Glendale 91206. (213) 245-8505.

COLORADO

This listing of continuing medical education programs in Colorado is compiled by the Denver Medical Society. To list CME programs here, please send information at least two months in advance to: Mr Robert L. Kennedy, Denver Medical Society, 1850 Williams Street, Denver, CO 80218; or telephone (303) 377-1850.

Brochures, course information, and registration forms are available from the contact person or organization.

August 16-17—**Pediatric Nursing Traineeship Program.** Children's Hospital, Denver. Mon-Tues. Contact: Outreach Office, (303) 861-6188.

August 16-19—**Respiratory Therapy Traineeship Program.** Children's Hospital, Denver. Mon-Thurs. Contact: Jeff Griebel, (303) 861-6668.

August 19-21—**3rd Annual Musculoskeletal Infection Society Meeting.** U of Colo at Snowmass Village. Thurs-Sat. Contact: U of Colo.

August 23-28—**18th Annual Primary Musculoskeletal Care Program.** U of Colo at The Village, Breckenridge. Mon-Sat. Contact: Phyllis Schroeder, U of Colo.

September 9-12—**Women in Medicine Third Annual Conference: Inventing Our Future.** Rose Medical Center at Westin Hotel, Vail. Thurs-Sun. Contact: Women in Medicine Conference, Rose Medical Center, (303) 770-2220.

September 20-21—**Pediatric Nursing Traineeship Program.** Children's Hospital, Denver, Mon-Tues. Contact: Outreach Office, (303) 861-6668.

September 21-22, 28-29—**Comprehensive Perinatal Nursing Course.** Children's Hospital at University Hospital, Denver. Tues-Wed. Contact: Trish Beachy, (303) 270-8376.

September 23-25—**The Penrose Cancer Conference: Neoplastic Diseases of the Breast and Ovary.** The Penrose-St Francis Healthcare System at the Broadmoor Hotel, Colorado Springs. Thurs-Sat. Contact: Deborah Hood, Penrose-St Francis Health Care System, PO Box 7021, Colorado Springs 80933-9939. (719) 630-5716.

September 24—**Health Care Reform: The Heart of the Matter.** St Anthony Hospitals and Rocky Mountain Heart Consortium at Scanticon Hotel & Conference Center, Englewood. Fri. Contact: Rocky Mountain Heart Consortium, (303) 393-3951.

October 14-16—**Rural Perinatal Traineeship Program.** Children's Hospital, Denver. Thurs-Sat. Contact: Outreach Office, (303) 861-6668.

November 5-6—**16th Annual Perinatal Conference.** Children's Hospital of Denver at Laramie, Wyoming. Fri-Sat. Contact: Conference Office, (303) 861-6946 or (800) 225-0010.

November 11-13—**Rural Perinatal Traineeship Program.** Children's Hospital, Denver. Thurs-Sat. Contact: Outreach Office, (303) 861-6668.

December 18—**Computers in Medicine.** Rose Medical Center at Hotel L'Ostello, Vail. Sat. Repeated weekly through April 23, 1994, at either Hotel L'Ostello, Vail, or Hotel Wildwood, Snowmass Village. Contact: Bernard Karshmer, (800) 525-5810.

First Wednesday of Each Month—**Various Topics in Neurology.** Sponsored by the Colorado Society of Clinical Neurologists. Contact: Colorado Society of Neurologists, (303) 449-3566.

CONTACT INFORMATION

U of Colo—Contact: University of Colorado School of Medicine, Office of Continuing Medical Education, 4200 E 9th Ave, Denver, CO. (303) 270-5195 or (800) 882-9153; FAX (303) 270-6761.

NEW MEXICO

Information, requests for accreditation, and items to be listed should be sent to the chair of the CME Committee, New Mexico Medical Society, 7770 Jefferson, Suite 400, Albuquerque, NM 87109, at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 828-0237.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

September 10-11—**New Mexico Chapter, American College of Surgeons Annual Meeting.** Holiday Inn Pyramid, Albuquerque. Fri-Sat. Contact: Bonnie Smith, 7770 Jefferson NE, #400, Albuquerque 87109. (505) 269-5883 or (505) 828-0237.

October 1-2—**John N. Wilson, MD, Lectureship in Cardiology: Cardiology '93.** Albuquerque Hilton Hotel. Fri-Sat. Contact: Mary Boning, PO Box 26666, Albuquerque 87125-6666. (505) 841-1225.

October 2-3—**Pediatric Sports Medicine and Fitness.** Inn of the Mountain Gods, Mescalero/Ruidoso. Sat-Sun. Contact: Richard Rolston, MD, 4808 McMahon Blvd NW, #16, Albuquerque 87114. (505) 898-7898.

October 16—**New Mexico Orthopaedic Association Annual Meeting: Sports Medicine.** Inn at Loretto, Santa Fe. Sat. Contact: Elsa Hall, 7770 Jefferson NE, #400, Albuquerque 87109. (505) 828-0237.

(Continued on Page 138)

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Dear Surgeon:

For the past five years, the American College of Surgeons, through its recently reorganized Program Committee, has been aggressively revising the annual Clinical Congress program. Revisions focus on the following key areas:

1. **Ensuring that the content of the scientific sessions reflect relevant and current surgical information and issues**
2. **Providing flexibility in the time and mode of presentation of the scientific sessions, in response to input from the fellowship**
3. **Developing interdisciplinary scientific sessions that the universal surgical specialty representation within the College allows and enhances**

It is our fondest hope that, as you review the content of the Clinical Congress program for 1993, you will agree with the Program Committee that this program is superlative. The program covers virtually the full spectrum of current scientific and socioeconomic subjects of broad interest to surgeons. The program also addresses many of the most recent advances and innovations in surgical science, presented by the foremost authorities in their respective fields.

With regard to the educational process, we are expanding the number of postgraduate courses that utilize electronic interaction between faculty and participants. The number of sessions for which on-site Clinitapes will be available is also greater this year.

We especially call your attention to our coverage of the following points of intense current interest:

- **Minimal access surgery**
- **Molecular biology**
- **Surgery of the breast**
- **Health care reform**
- **Ambulatory surgery**
- **Interdisciplinary sessions**

San Francisco will be the setting for this exciting program in October, and we hope you will attend. See you there!

Best personal regards,

Seymour I. Schwartz, MD, FACS
Chairman, Program Committee

Gerald O. Strauch, MD, FACS
Director, Assembly Department

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All manuscripts will be subject to peer review.

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All authors must sign the letter of transmittal, with one author designated as correspondent and his or her name, address, and telephone number included.

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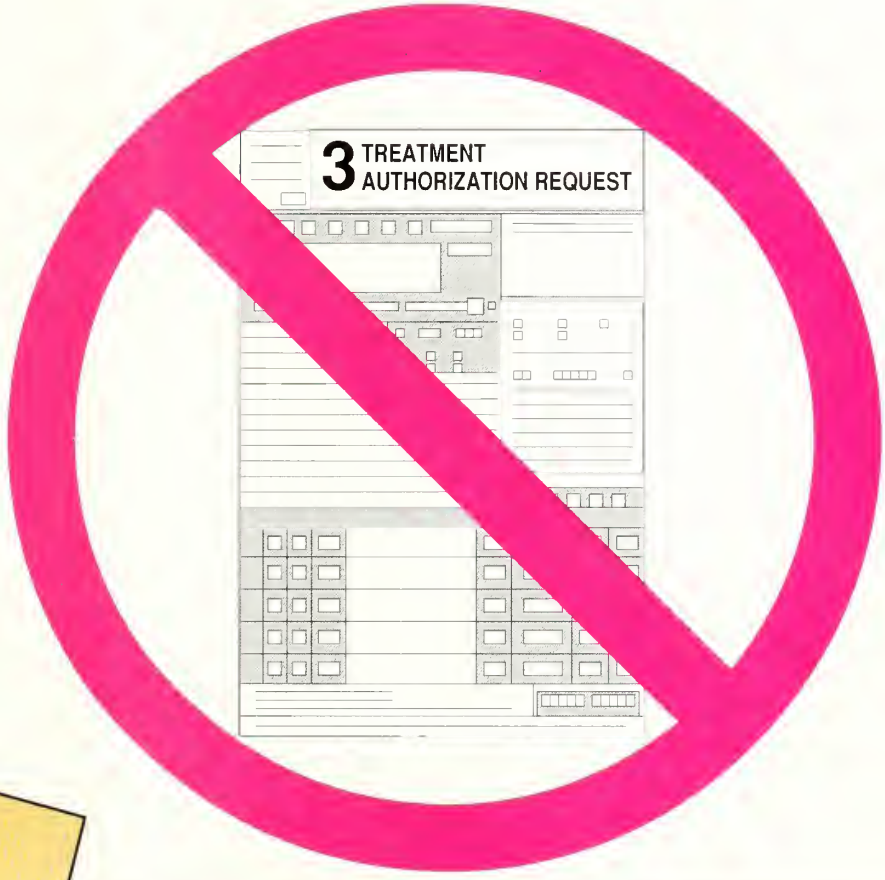
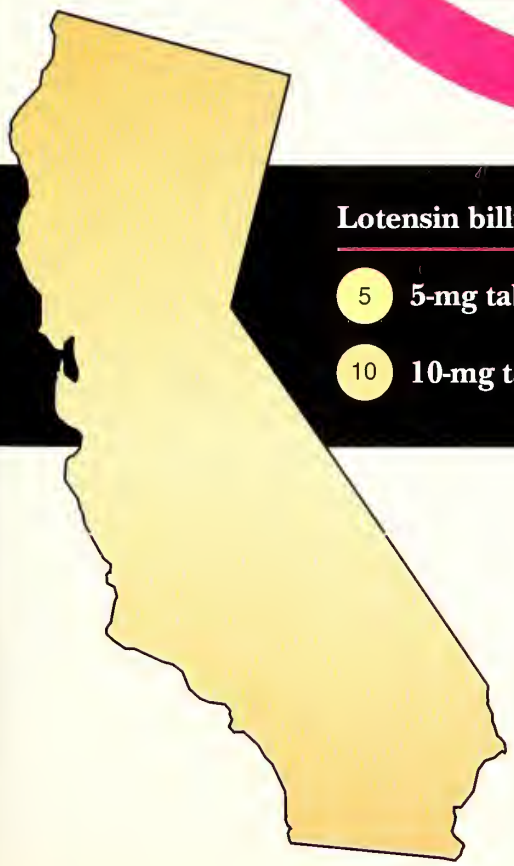
- Illustrations, black and white glossy, identified with lead author's name—3 sets, plus figure legends that describe fully and in complete sentences what the figure depicts
- Letter of transmittal that includes release of copyright, statement of conflict of interest, and authorship responsibility, **signed by all authors**
- A 200-word abstract
- Title page that includes current affiliation of all authors and address **and telephone number** for corresponding author
- Permission-to-borrow letters for any previously published illustrations or tables
- All references numbered consecutively, double-spaced, in *WJM* style, and cited in text. No unpublished data or nonscientific publications listed in references (include in text)

Freedom from Medi-Cal TARs— with Lotensin

Effective 7/1/93, Lotensin is 1 of only 3 ACE inhibitors approved for use without a TAR*





Lotensin billing codes

5	5-mg tablets	CP 3138 B	20	20-mg tablets	CP 3138 F
10	10-mg tablets	CP 3138 D	40	40-mg tablets	CP 3138 J

Lotensin®

benazepril HCl

*Exception: If a patient has been on "continuing care" with a drug that has been deleted from the *Medi-Cal List of Contract Drugs*, he or she may continue to receive that drug without prior authorization. See *Medi-Cal Pharmacy Bulletin No. 315*.

Please see complete Prescribing Information on following page.

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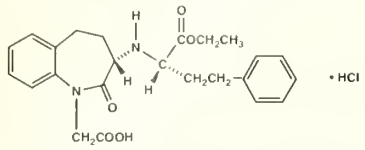
Lotensin®

benazepril hydrochloride
Tablets

Prescribing Information

Use in Pregnancy
When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, Lotensin should be discontinued as soon as possible. See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

DESCRIPTION
Benazepril hydrochloride is a white to off-white crystalline powder, soluble (>100 mg/mL) in water, in ethanol, and in methanol. Benazepril's chemical name is 3-[[1-(ethoxy-carbonyl)-3-phenyl-(1S)-propyl]amino]-2,3,4,5-tetrahydro-2-oxo-1*H*-1-(3S)-benzazepine-1-acetic acid monohydrochloride, its structural formula is:



Its empirical formula is $C_{24}H_{28}N_2O_5$•HCl, and its molecular weight is 460.96
Benazeprilat, the active metabolite of benazepril, is a non-sulfhydryl angiotensin-converting enzyme inhibitor. Benazepril is converted to benazeprilat by hepatic cleavage of the ester group.

Lotensin is supplied as tablets containing 5 mg, 10 mg, 20 mg, and 40 mg of benazepril for oral administration. The inactive ingredients are cellulose compounds, colloidal silicon dioxide, crospovidone, hydrogenated castor oil (5-mg, 10-mg, and 20-mg tablets), iron oxides, lactose, magnesium stearate (40-mg tablets), polysorbate 80, propylene glycol (5-mg and 40-mg tablets), starch, talc, and titanium dioxide.

CLINICAL PHARMACOLDGY
Mechanism of Action
Benazepril and benazeprilat inhibit angiotensin-converting enzyme (ACE) in human subjects and animals. ACE is a peptidyl dipeptidase that catalyzes the conversion of angiotensin I to the vasoconstrictor substance, angiotensin II. Angiotensin II also stimulates aldosterone secretion by the adrenal cortex.

Inhibition of ACE results in decreased plasma angiotensin II, which leads to decreased vasopressor activity and to decreased aldosterone secretion. The latter decrease may result in a small increase of serum potassium. Hypertensive patients treated with Lotensin alone for up to 52 weeks had elevations of serum potassium of up to 0.2 mEq/L. Similar patients treated with Lotensin and hydrochlorothiazide for up to 24 weeks had no consistent changes in their serum potassium (see PRECAUTIONS).

Removal of angiotensin II negative feedback on renin secretion leads to increased plasma renin activity. In animal studies, benazepril had no inhibitory effect on the vasopressor response to angiotensin II and did not interfere with the hemodynamic effects of the autonomic neurotransmitters acetylcholine, epinephrine, and norepinephrine.

ACE is identical to kininase, an enzyme that degrades bradykinin. Whether increased levels of bradykinin, a potent vasodepressor peptide, play a role in the therapeutic effects of Lotensin remains to be elucidated.

While the mechanism through which benazepril lowers blood pressure is believed to be primarily suppression of the renin-angiotensin-aldosterone system, benazepril has an antihypertensive effect even in patients with low-renin hypertension. In particular, Lotensin was antihypertensive in all races studied, although it was somewhat less effective in blacks than in nonblacks.

Pharmacokinetics and Metabolism
Following oral administration of Lotensin, peak plasma concentrations of benazepril are reached within 0.5-1.0 hours. The extent of absorption is at least 37% as determined by urinary recovery and is not significantly influenced by the presence of food in the GI tract.

Cleavage of the ester group (primarily in the liver) converts benazepril to its active metabolite, benazeprilat. Peak plasma concentrations of benazeprilat are reached 1-2 hours after drug intake in the fasting state and 2-4 hours after drug intake in the nonfasting state. The serum protein binding of benazepril is about 96.7% and that of benazeprilat about 95.3%, as measured by equilibrium dialysis; on the basis of in vitro studies, the degree of protein binding should be unaffected by age, hepatic dysfunction, or concentration (over the concentration range of 0.24-23.6 μmol/L).

Benazepril is almost completely metabolized to benazeprilat, which has much greater ACE inhibitory activity than benazepril, and to the glucuronide conjugates of benazepril and benazeprilat. Only trace amounts of an administered dose of Lotensin can be recovered in the urine as unchanged benazepril, while about 20% of the dose is excreted as benazeprilat, 4% as benazepril glucuronide, and 8% as benazeprilat glucuronide.

The kinetics of benazepril are approximately dose-proportional within the dosage range of 10-80 mg.

The effective half-life of accumulation of benazeprilat following multiple dosing of benazepril hydrochloride is 10-11 hours. Thus, steady-state concentrations of benazeprilat should be reached after 2 or 3 doses of benazepril hydrochloride given once daily.

The kinetics did not change, and there was no significant accumulation during chronic administration (28 days) of once-daily doses between 5 mg and 20 mg. Accumulation ratios based on AUC and urinary recovery of benazeprilat were 1.19 and 1.27, respectively.

When dialysis was started two hours after ingestion of 10 mg of benazepril, approximately 6% of benazeprilat was removed in 4 hours of dialysis. The parent compound, benazepril, was not detected in the dialysate.

The disposition of benazepril and benazeprilat in patients with mild-to-moderate renal insufficiency (creatinine clearance >30 mL/min) is similar to that in patients with normal renal function. In patients with creatinine clearance ≤30 mL/min, peak benazeprilat levels and the initial (alpha phase) half-life increase, and time to steady state may be delayed (see DOSAGE AND ADMINISTRATION).

Benazepril and benazeprilat are cleared predominantly by renal excretion in healthy subjects with normal renal function. Nonrenal (i.e., biliary) excretion accounts for approximately 11-12% of benazeprilat excretion in healthy subjects. In patients with renal failure, biliary clearance may compensate to an extent for deficient renal clearance.

In patients with hepatic dysfunction due to cirrhosis, levels of benazeprilat are essentially unaltered. The pharmacokinetics of benazepril and benazeprilat do not appear to be influenced by age.

In studies in rats given ^{14}C-benazepril, benazepril and its metabolites crossed the blood-brain barrier only to an extremely low extent. Multiple doses of benazepril did not result in accumulation in any tissue except the lung, where, as with other ACE inhibitors in similar studies, there was a slight increase in concentration due to slow elimination in that organ.

Some placental passage occurred when the drug was administered to pregnant rats.

Pharmacodynamics
Single and multiple doses of 10 mg or more of Lotensin cause inhibition of plasma ACE activity by at least 80-90% for at least 24 hours after dosing. Pressor responses to exogenous angiotensin I were inhibited by 60-90% (up to 4 hours post-dose) at the10 mg dose.

Administration of Lotensin to patients with mild-to-moderate hypertension results in a reduction of both supine and standing blood pressure to about the same extent with no compensatory tachycardia. Symptomatic postural hypotension is infrequent, although it can occur in patients who are salt- and/or volume-depleted (see WARNINGS).

In single-dose studies, Lotensin lowered blood pressure within 1 hour, with peak reductions achieved 2-4 hours after dosing. The antihypertensive effect of a single dose persisted for 24 hours. In multiple-dose studies, once-daily doses of 20-80 mg decreased seated pressure (systolic/diastolic) 24 hours after dosing by about 6-12/4-7 mmHg. The trough values represent reductions of about 50% of that seen at peak.

Four dose-response studies using once-daily dosing were conducted in 470 mild-to-moderate hypertensive patients not using diuretics. The minimal effective once-daily dose of Lotensin was 10 mg; but further falls in blood pressure, especially at morning trough, were seen with higher doses in the studied dosing range (10-80 mg). In studies comparing the same daily dose of Lotensin given as a single morning dose or as a twice-daily dose, blood pressure reductions at the time of morning trough blood levels were greater with the divided regimen.

During chronic therapy, the maximum reduction in blood pressure with any dose is generally achieved after 1-2 weeks. The antihypertensive effects of Lotensin have continued during therapy for at least two years. Abrupt withdrawal of Lotensin has not been associated with a rapid increase in blood pressure.

In patients with mild-to-moderate hypertension, Lotensin 10-20 mg was similar in effectiveness to captopril, hydrochlorothiazide, nifedipine SR, and propranolol.

The antihypertensive effects of Lotensin were not appreciably different in patients receiving high- or low-sodium diets.

In hemodynamic studies in dogs, blood pressure reduction was accompanied by a reduction in peripheral arterial resistance, with an increase in cardiac output and renal blood flow and little or no change in heart rate. In normal human volunteers, single doses of benazepril caused an increase in renal blood flow but had no effect on glomerular filtration rate.

Use of Lotensin in combination with thiazide diuretics gives a blood-pressure-lowering effect greater than that seen with either agent alone. By blocking the renin-angiotensin-aldosterone axis, administration of Lotensin tends to reduce the potassium loss associated with the diuretic.

INDICATIDNS AND USAGE
Lotensin is indicated for the treatment of hypertension. It may be used alone or in combination with thiazide diuretics.

In using Lotensin, consideration should be given to the fact that another angiotensin-converting enzyme inhibitor, captopril, has caused agranulocytosis, particularly in patients with renal impairment or collagen-vascular disease. Available data are insufficient to show that Lotensin does not have a similar risk (see WARNINGS).

CONTRAINDICATIONS
Lotensin is contraindicated in patients who are hypersensitive to this product or to any other ACE inhibitor.

WARNINGS
Angioedema
Angioedema of the face, extremities, lips, tongue, glottis, and larynx has been reported in patients treated with angiotensin-converting enzyme inhibitors. In U.S. clinical trials, symptoms consistent with angioedema were seen in none of the subjects who received placebo and in about 0.5% of the subjects who received Lotensin. Angioedema associated with laryngeal edema can be fatal. If laryngeal stridor or angioedema of the face, tongue, or glottis occurs, treatment with Lotensin should be discontinued and appropriate therapy instituted immediately. **Where there is involvement of the tongue, glottis, or larynx, likely to cause airway obstruction, appropriate therapy, e.g., subcutaneous epinephrine injection 1:1000 (0.3 mL to 0.5 mL) should be promptly administered (see ADVERSE REACTIONS).**

Hypotension
Lotensin can cause symptomatic hypotension. Like other ACE inhibitors, benazepril has been only rarely associated with hypotension in uncomplicated hypertensive patients. Symptomatic hypotension is most likely to occur in patients who have been volume- and/or salt-depleted as a result of prolonged diuretic therapy, dietary salt restriction, dialysis, diarrhea, or vomiting. Volume- and/or salt-depletion should be corrected before initiating therapy with Lotensin.

In patients with congestive heart failure, with or without associated renal insufficiency, ACE inhibitor therapy may cause excessive hypotension, which may be associated with oliguria or azotemia and, rarely, with acute renal failure and death. In such patients, Lotensin therapy should be started under close medical supervision, they should be followed closely for the first 2 weeks of treatment and whenever the dose of benazepril or diuretic is increased.

If hypotension occurs, the patient should be placed in a supine position, and, if necessary, treated with intravenous infusion of physiological saline. Lotensin treatment usually can be continued following restoration of blood pressure and volume.

Neutropenia/Agranulocytosis
Another angiotensin-converting enzyme inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression, rarely in uncomplicated patients, but more frequently in patients with renal impairment, especially if they also have a collagen-vascular disease such as systemic lupus erythematosus or scleroderma. Available data from clinical trials of benazepril are insufficient to show that benazepril does not cause agranulocytosis at similar rates. Monitoring of white blood cell counts should be considered in patients with collagen-vascular disease, especially if the disease is associated with impaired renal function.

Fetal/Neonatal Morbidity and Mortality
ACE inhibitors can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature. When pregnancy is detected, ACE inhibitors should be discontinued as soon as possible.

The use of ACE inhibitors during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to the ACE inhibitor exposure.

These adverse effects do not appear to have resulted from intrauterine ACE inhibitor exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to ACE inhibitors only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should make every effort to discontinue the use of benazepril as soon as possible.

Rarely (probably less often than once in every thousand pregnancies), no alternative to ACE inhibitors will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intraamniotic environment.

If oligohydramnios is observed, benazepril should be discontinued unless it is considered life-saving for the mother. Contraction stress testing (CST), a nonstress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of *in utero* exposure to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function. Benazepril, which crosses the placenta, can theoretically be removed from the neonatal circulation by these means; there are occasional reports of benefit from these maneuvers with another ACE inhibitor, but experience is limited.

No teratogenic effects of Lotensin were seen in studies of pregnant rats, mice, and rabbits. On a mg/m^2 basis, the doses used in these studies were 60 times (in rats), 9 times (in mice), and more than 0.8 times (in rabbits) the maximum recommended human dose (assuming a 50 kg woman). On a mg/kg basis these multiples are 300 times (in rats), 90 times (in mice) and more than 3 times (in rabbits) the maximum recommended human dose.

PRECAUTIONS
General
Impaired Renal Function: As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe congestive heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with angiotensin-converting enzyme inhibitors, including Lotensin, may be associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death. In a small study of hypertensive patients with renal artery stenosis in a solitary kidney or bilateral renal artery stenosis, treatment with Lotensin was associated with increases in blood urea nitrogen and serum creatinine; these increases were reversible upon discontinuation of Lotensin or diuretic therapy, or both. When such patients are treated with ACE inhibitors, renal function should be monitored during the first few weeks of therapy. Some hypertensive patients with no apparent preexisting renal vascular disease have developed increases in blood urea nitrogen and serum creatinine, usually minor and transient, especially when Lotensin has been given concomitantly with a diuretic. This is more likely to occur in patients with preexisting renal impairment. Dosage reduction of Lotensin and/or discontinuation of the diuretic may be required. **Evaluation of the hypertensive patient should always include assessment of renal function (see DOSAGE AND ADMINISTRATION).**

Hemodialysis Patients: Anaphylactoid reactions have been reported in patients dialyzed with high-flux membranes and treated concomitantly with an ACE inhibitor. In these patients, consideration should be given to using a different type of dialysis membrane or a different class of antihypertensive agent.

Hyperkalemia: In clinical trials, hyperkalemia (serum potassium at least 0.5 mEq/L greater than the upper limit of normal) occurred in approximately 1% of hypertensive patients receiving Lotensin. In most cases, these were isolated values which resolved despite continued therapy. Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with Lotensin (see Drug Interactions).

Cough: Cough has been reported with the use of ACE inhibitors. Characteristically, the cough is nonproductive, persistent, and resolves after discontinuation of therapy. ACE inhibitor-induced cough should be considered as part of the differential diagnosis of cough.

Impaired Liver Function: In patients with hepatic dysfunction due to cirrhosis, levels of benazeprilat are essentially unaltered.

Surgery/Anesthesia: In patients undergoing surgery or during

anesthesia with agents that produce hypotension, benazepril will block the angiotensin II formation that could otherwise occur secondary to compensatory renin release. Hypotension that occurs as a result of this mechanism can be corrected by volume expansion.

Information for Patients

Pregnancy: Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to ACE inhibitors, and they should also be told that these consequences do not appear to have resulted from intrauterine ACE inhibitor exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.

Angioedema: Angioedema, including laryngeal edema, can occur with treatment with ACE inhibitors, especially following the first dose. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, eyes, lips, or tongue, or difficulty in breathing) and to take no more drug until they have consulted with the prescribing physician.

Symptomatic Hypotension: Patients should be cautioned that lightheadedness can occur, especially during the first days of therapy, and it should be reported to the prescribing physician. Patients should be told that if syncope occurs, Lotensin should be discontinued until the prescribing physician has been consulted.

All patients should be cautioned that inadequate fluid intake or excessive perspiration, diarrhea, or vomiting can lead to an excessive fall in blood pressure, with the same consequences of lightheadedness and possible syncope.

Hyperkalemia: Patients should be told not to use potassium supplements or salt substitutes containing potassium without consulting the prescribing physician.

Neutropenia: Patients should be told to promptly report any indication of infection (e.g., sore throat, fever), which could be a sign of neutropenia.

Drug Interactions

Diuretics: Patients on diuretics, especially those in whom diuretic therapy was recently instituted, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with Lotensin. The possibility of hypotensive effects with Lotensin can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with Lotensin. If this is not possible, the starting dose should be reduced (see DOSAGE AND ADMINISTRATION).

Potassium Supplements and Potassium-Sparing Diuretics: Lotensin can attenuate potassium loss caused by thiazide diuretics. Potassium-sparing diuretics (spironolactone, amiloride, triamterene, and others) or potassium supplements can increase the risk of hyperkalemia. Therefore, if concomitant use of such agents is indicated, they should be given with caution, and the patient's serum potassium should be monitored frequently.

Oral Anticoagulants: Interaction studies with warfarin and acenocoumarol failed to identify any clinically important effects on the serum concentrations or clinical effects of these anticoagulants.

Lithium: Increased serum lithium levels and symptoms of lithium toxicity have been reported in patients receiving ACE inhibitors during therapy with lithium. These drugs should be coadministered with caution, and frequent monitoring of serum lithium levels is recommended. If a diuretic is also used, the risk of lithium toxicity may be increased.

Other: No clinically important pharmacokinetic interactions occurred when Lotensin was administered concomitantly with hydrochlorothiazide, chlorthalidone, furosemide, digoxin, propranolol, atenolol, naproxen, or cimetidine.

Lotensin has been used concomitantly with beta-adrenergic-blocking agents, calcium-channel-blocking agents, diuretics, digoxin, and hydralazine, without evidence of clinically important adverse interactions. Benazepril, like other ACE inhibitors, has had less than additive effects with beta-adrenergic blockers, presumably because both drugs lower blood pressure by inhibiting parts of the renin-angiotensin system.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No evidence of carcinogenicity was found when benazepril was administered to rats and mice for up to two years at doses of up to 150 mg/kg/day. When compared on the basis of body weights, this dose is 110 times the maximum recommended human dose. When compared on the basis of body surface areas, this dose is 18 and 9 times (rats and mice, respectively) the maximum recommended human dose (calculations assume a patient weight of 60 kg). No mutagenic activity was detected in the Ames test in bacteria (with or without metabolic activation), in an in vitro test for forward mutations in cultured mammalian cells, or in a nucleus anomaly test. In doses of 50-500 mg/kg/day (6-60 times the maximum recommended human dose based on mg/m^2 comparison and 37-375 times the maximum recommended human dose based on a mg/kg comparison), Lotensin had no adverse effect on the reproductive performance of male and female rats.

Pregnancy Categories C (first trimester) and D (second and third trimesters)

See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

Nursing Mothers

Minimal amounts of unchanged benazepril and of benazeprilat are excreted into the breast milk of lactating women treated with benazepril. A newborn child ingesting entirely breast milk would receive less than 0.1% of the mg/kg maternal dose of benazepril and benazeprilat.

Geriatric Use

Of the total number of patients who received benazepril in U.S. clinical studies of Lotensin, 18% were 65 or older while 2% were 75 or older. No overall differences in effectiveness or safety were observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Pediatric Use

Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Lotensin has been evaluated for safety in over 6000 patients with hypertension; over 700 of these patients were treated for at least one year. The overall incidence of reported adverse events was comparable in Lotensin and placebo patients.

The reported side effects were generally mild and transient, and there was no relation between side effects and age, duration of therapy, or total dosage within the range of 2 to 80 mg. Discontinuation of therapy because of a side effect was required in approximately 5% of U.S. patients treated with Lotensin and in 3% of patients treated with placebo.

The most common reasons for discontinuation were headache (0.6%) and cough (0.5%). (see PRECAUTIONS, Cough).

The side effects considered possibly or probably related to study drug that occurred in U.S. placebo-controlled trials in more than 1% of patients treated with Lotensin are shown below.

PATIENTS IN U.S. PLACEBO-CONTROLLED STUDIES

	LOTENSIN (N=964)		PLACEBO (N=496)	
	N	%	N	%
Headache	60	6.2	21	4.2
Dizziness	35	3.6	12	2.4
Fatigue	23	2.4	11	2.2
Somnolence	15	1.6	2	0.4
Postural Dizziness	14	1.5	1	0.2
Nausea	13	1.3	5	1.0
Cough	12	1.2	5	1.0

Other adverse experiences reported in controlled clinical trials (in less than 1% of benazepril patients), and rarer events seen in postmarketing experience, include the following (in some, a causal relationship to drug use is uncertain):

Cardiovascular: Symptomatic hypotension was seen in 0.3% of patients, postural hypotension in 0.4%, and syncope in 0.1%; these reactions led to discontinuation of therapy in 4 patients who had received benazepril monotherapy and in 9 patients who had received benazepril with hydrochlorothiazide (see PRECAUTIONS and WARNINGS). Other reports included angina pectoris, palpitations, and peripheral edema.

Renal: Of hypertensive patients with no apparent preexisting renal disease, about 2% have sustained increases in serum creatinine to at least 150% of their baseline values while receiving Lotensin, but most of these increases have disappeared despite continuing treatment. A much smaller fraction of these patients (less than 0.1%) developed simultaneous (usually transient) increases in blood urea nitrogen and serum creatinine.

Fetal/Neonatal Morbidity and Mortality: See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

Angioedema: Angioedema has been reported in patients receiving ACE inhibitors. During clinical trials in hypertensive patients with benazepril, 0.5% of patients experienced edema of the lips or face without other manifestations of angioedema. Angioedema associated with laryngeal edema and/or shock may be fatal. If angioedema of the face, extremities, lips, tongue, or glottis and/or larynx occurs, treatment with Lotensin should be discontinued and appropriate therapy instituted immediately (see WARNINGS).

Gastrointestinal: Constipation, gastritis, vomiting, and melena.

Dermatologic: Apparent hypersensitivity reactions (manifested by dermatitis, pruritus, or rash), photosensitivity, and flushing.

Neurologic and Psychiatric: Anxiety, decreased libido, hypertonia, insomnia, nervousness, and paresthesia.

Other: Arthralgia, arthritis, asthenia, asthma, bronchitis, dyspnea, impotence, infection, myalgia, sinusitis, sweating, and urinary tract infection.

Clinical Laboratory Test Findings

Creatinine and Blood Urea Nitrogen: Of hypertensive patients with no apparent preexisting renal disease, about 2% have sustained increases in serum creatinine to at least 150% of their baseline values while receiving Lotensin, but most of these increases have disappeared despite continuing treatment. A much smaller fraction of these patients (less than 0.1%) developed simultaneous (usually transient) increases in blood urea nitrogen and serum creatinine. None of these increases required discontinuation of treatment. Increases in these laboratory values are more likely to occur in patients with renal insufficiency or those pretreated with a diuretic and, based on experience with other ACE inhibitors, would be expected to be especially likely in patients with renal artery stenosis (see PRECAUTIONS, General).

Potassium: Since benazepril decreases aldosterone secretion, elevation of serum potassium can occur. Potassium supplements and potassium-sparing diuretics should be given with caution, and the patient's serum potassium should be monitored frequently (see PRECAUTIONS).

Hemoglobin: Decreases in hemoglobin (a low value and a decrease of 5 g/dL) were rare, occurring in only 1 of 2014 patients receiving Lotensin alone and in 1 of 1357 patients receiving Lotensin plus a diuretic. No U.S. patients discontinued treatment because of decreases in hemoglobin.

Other (causal relationships unknown): Clinically important changes in standard laboratory tests were rarely associated with Lotensin administration. Elevations of liver enzymes, serum bilirubin, uric acid, and blood glucose have been reported, as have scattered incidents of hyponatremia, electrocardiographic changes, leukopenia, eosinophilia, and proteinuria. In U.S. trials, less than 0.5% of patients discontinued treatment because of laboratory abnormalities.

OVERDOSAGE

Single oral doses of 3 g/kg benazepril were associated with significant lethality in mice. Rats, however, tolerated single oral doses of up to 6 g/kg. Reduced activity was seen at 1 g/kg in mice and at 5 g/kg in rats. Human overdoses of benazepril have not been reported, but the most common manifestation of human benazepril overdosage is likely to be hypotension.

Laboratory determinations of serum levels of benazepril and its metabolites are not widely available, and such determinations have, in any event, no established role in the management of benazepril overdose.

No data are available to suggest physiological maneuvers (e.g., maneuvers to change the pH of the urine) that might accelerate elimination of benazepril and its metabolites. Benazepril is only slightly dialyzable, but dialysis might be considered in overdosed patients with severely impaired renal function (see PRECAUTIONS, Hemodialysis Patients).

Angiotensin II could presumably serve as a specific antagonist-antidote in the setting of benazepril overdose, but angiotensin II is essentially unavailable outside of scattered research facilities. Because the hypotensive effect of benazepril is achieved through vasodilation and effective hypovolemia, it is reasonable to treat benazepril overdose by infusion of normal saline solution.

DOSAGE AND ADMINISTRATION

The recommended initial dose for patients not receiving a diuretic is 10 mg once-a-day. The usual maintenance dosage range is 20-40 mg per day administered as a single dose or in two equally divided doses. A dose of 80 mg gives an increased response, but experience with this dose is limited. The divided regimen was more effective in controlling trough (pre-dosing) blood pressure than the same dose given as a once-daily regimen. Dosage adjustment should be based on measurement of peak (2-6 hours after dosing) and trough responses. If a once-daily regimen does not give adequate trough response an increase in dosage or divided administration should be considered. If blood pressure is not controlled with Lotensin alone, a diuretic can be added.

Total daily doses above 80 mg have not been evaluated.

Concomitant administration of Lotensin with potassium supplements, potassium salt substitutes, or potassium-sparing diuretics can lead to increases of serum potassium (see PRECAUTIONS).

In patients who are currently being treated with a diuretic, symptomatic hypotension occasionally can occur following the initial dose of Lotensin. To reduce the likelihood of hypotension, the diuretic should, if possible, be discontinued two to three days prior to beginning therapy with Lotensin (see WARNINGS). Then, if blood pressure is not controlled with Lotensin alone, diuretic therapy should be resumed.

If the diuretic cannot be discontinued, an initial dose of 5 mg Lotensin should be used to avoid excessive hypotension.

Dosage Adjustment in Renal Impairment

For patients with a creatinine clearance <30 mL/min/1.73 m^2 (serum creatinine >3 mg/dL), the recommended initial dose is 5 mg Lotensin once daily. Dosage may be titrated upward until blood pressure is controlled or to a maximum total daily dose of 40 mg (see PRECAUTIONS, Hemodialysis Patients).

HOW SUPPLIED

Lotensin is available in tablets of 5 mg, 10 mg, 20 mg, and 40 mg, packaged with a desiccant in bottles of 100 tablets. Lotensin is also supplied in blister packages (1 tablet/blister), in Accu-Pak® Unit Dose boxes containing 10 strips of 10 blisters each.

Each tablet is imprinted with LOTENSIN on one side and the tablet strength ("5", "10", "20", or "40") on the other. Samples, when available, are identified by the word *SAMPLE* on each tablet.

The National Drug Codes for the various packages are:

Dose	Tablet Color	Bottle of 100	Accu-Pak® of 100
5 mg	light yellow	NDC 0083-0059-30	NDC 0083-0059-32
10 mg	dark yellow	NDC 0083-0063-30	NDC 0083-0063-32
20 mg	tan	NDC 0083-0079-30	NDC 0083-0079-32
40 mg	dark rose	NDC 0083-0094-30	NDC 0083-0094-32

Storage: Do not store above 86° F (30° C). Protect from moisture.

Dispense in tight container (USP).

Printed in U.S.A. C92-44 (Rev. 10/92)

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Dr Schriock is Assistant Clinical Professor, Department of Obstetrics, Gynecology, and Reproductive Sciences, University of California, San Francisco, School of Medicine.

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Dr Smith is Associate Editor of The Western Journal of Medicine.

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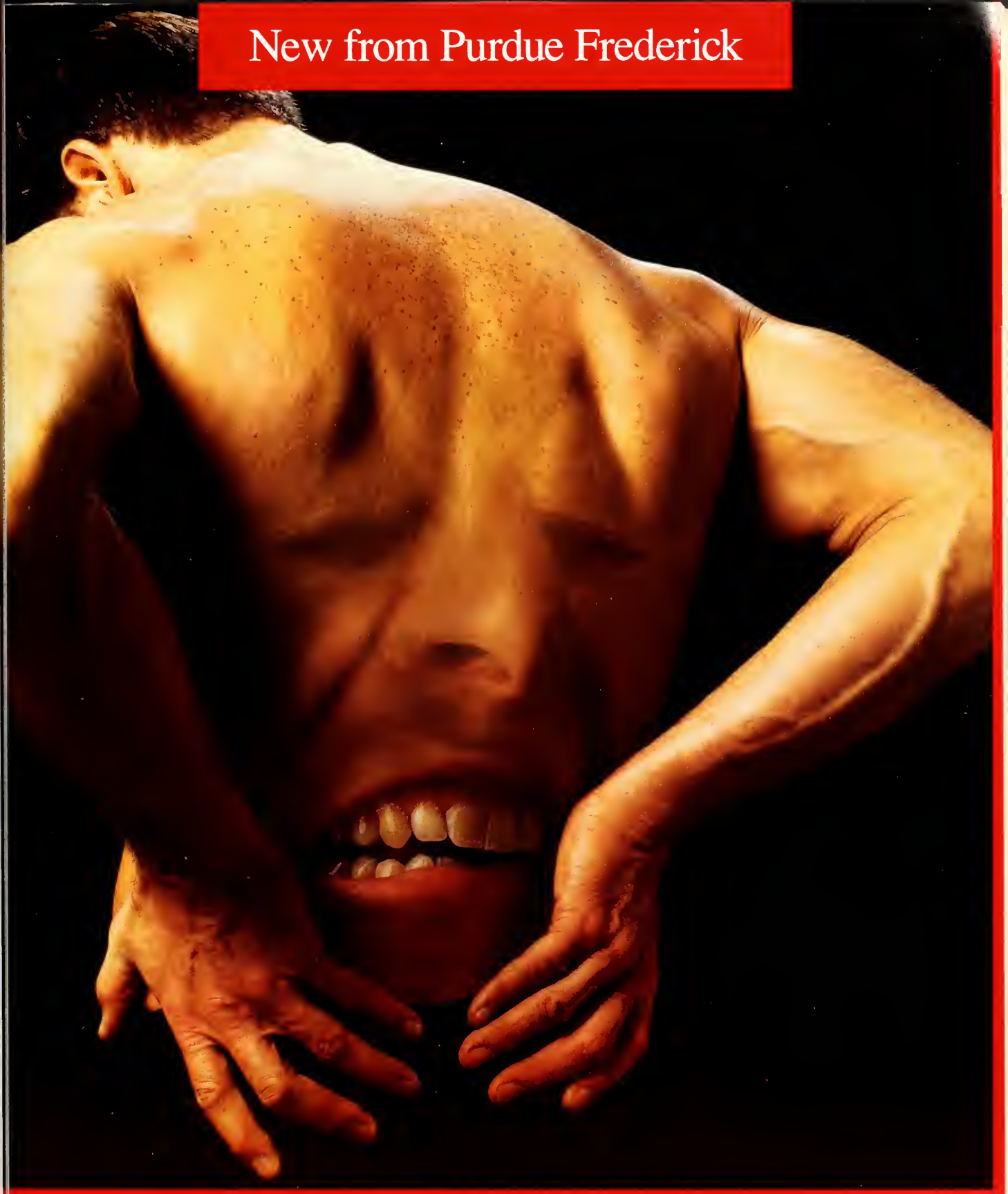
★ Affiliated Clinical Investigation Societies: the Western Association of Physicians; the Western Society for Clinical Investigation; the Western Section, American Federation for Clinical Research; the Western Society for Pediatric Research; the Western Region, Society for Investigative Dermatology.



Rapid, potent pain relief

Please read the brief summary of the prescribing information on the last page of this advertisement.

Introducing DHC plus™ CIII

A rational combination for pain relief...

Rapid, potent, pain-fighting triad

Unique 3-way action formula speeds strong, potentiated relief of *moderate to moderately severe pain.*

Each capsule contains:

dihydrocodeine bitartrate (16 mg)
Higher relative analgesic potency than codeine,[1-5] with few adverse reactions at recommended doses.[6]

acetaminophen (356.4 mg)
Provides peripherally acting analgesia that is safer than aspirin.[7] In combination, its significant opioid dose-sparing effects may reduce opioid adverse reactions.[8-10]

caffeine (30 mg)
Decreases drowsiness and fatigue,[11,12] and, in combination with an opioid, may counter sedation.[13] Potentiates acetaminophen analgesia.[12,14] Speeds onset of analgesic action.[12]

...without added adverse effects

- Rational combination of analgesics[8,12,15] may reduce adverse effects.[8-10,13]

Ideal for a range of patients

- **DHC plus™** capsules contain dihydrocodeine, a potent opioid that has 4 decades of clinical experience and a proven record of safety.[3]
- **DHC plus™** capsules can be prescribed for patients with aspirin sensitivity, asthma, and those taking anticoagulants.

Well accepted

- Easy-to-remember, flexible dosing: 2 capsules every 4 hours as needed for moderate to moderately severe pain.
- Easy-to-swallow capsules.

Because pain doesn't keep office hours

- **Telephone prescription and refills in most states** afford *comfort*—weekends, holidays, after-hours.
- **No triplicate-prescription** requirement offers *convenience*—no additional paperwork.
- **Flexible dosing schedule** provides *control*—2 capsules every 4 hours as needed for pain.
- **Renewable up to 5 times within 6 months** for *continuity*—uninterrupted pain management for extended-care situations.

The maximum daily dose of DHC plus™ CIII capsules provide more milligrams of analgesic than any CIII duo-combination.[6,15,16]

DHCplus™ CIII

dihydrocodeine bitartrate 16 mg
(Warning: may be habit forming.)
acetaminophen 356.4 mg
caffeine 30 mg

Because they can't wait for pain relief.

No matter where it hurts…
No matter when it hurts…
Rapid, potent pain relief

Brief Summary on DHC Plus™ CIII Capsules

Before prescribing, see complete prescribing information.

DHC Plus™ capsules

Each capsule contains:

Dihydrocodeine Bitartrate ..... 16 mg

(**Warning:** May be habit forming.)

Acetaminophen..... 356.4 mg

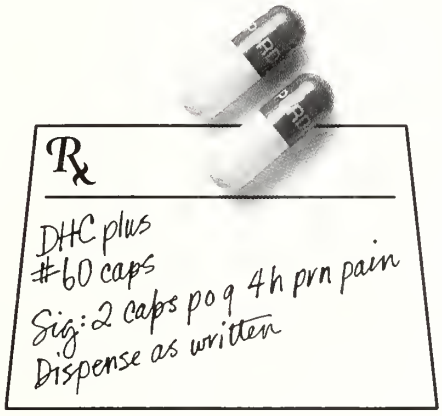
Caffeine ..... 30 mg

INDICATIONS: For the relief of moderate to moderately severe pain.

CONTRAINDICATIONS: Hypersensitivity to dihydrocodeine, codeine, or acetaminophen.

WARNINGS: Usage In Ambulatory Patients: Dihydrocodeine may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. The patient using DHC Plus™ should be cautioned accordingly.

Interactions with other Central Nervous System Depressants: Patients receiving other narcotic analgesics, general anesthetics, tranquilizers, sedative-hypnotics, or other CNS depressants (including alcohol) concomitantly with DHC Plus™ may exhibit an additive CNS depression. When such combined therapy is contemplated, the dose of one or both agents should be reduced.



PRECAUTIONS: General: DHC Plus™ should be given with caution to certain patients such as the elderly or debilitated.

Drug Interactions: The CNS-depressant effects of dihydrocodeine bitartrate may be additive with that of other CNS depressants. See "Warnings."

Usage In Pregnancy: Reproduction studies have not been performed in animals. There is no adequate information on whether this drug may affect fertility in human males and females or has a teratogenic potential or other adverse effect on the fetus.

Usage In Children: Since there is no experience in children who have received this drug, safety and efficacy in children have not been established.

ADVERSE REACTIONS: The most frequently observed reactions include light-headedness, dizziness, drowsiness, sedation, nausea, vomiting, constipation, pruritus, and skin reactions.

DRUG ABUSE AND DEPENDENCE: DHC Plus™ is subject to the provisions of the Controlled Substance Act, and has been placed in Schedule III.

Dihydrocodeine can produce drug dependence of the codeine type and therefore has the potential of being abused. Psychic dependence, physical dependence, and tolerance may develop upon repeated administration of dihydrocodeine, and it should be prescribed and administered with the same degree of caution appropriate to the use of other oral narcotic-containing medications.

OVERDOSAGE: Dihydrocodeine: Signs and Symptoms: Serious overdose with DHC Plus™ is characterized by respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), extreme somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, and sometimes bradycardia and hypotension. In severe overdosage, apnea, circulatory collapse, cardiac arrest and death may occur.

Treatment: Primary attention should be given to the re-establishment of adequate respiratory exchange through provision of a patent airway and the institution of assisted or controlled ventilation. The narcotic antagonist naloxone is a specific antidote against respiratory depression which may result from overdosage or unusual sensitivity to narcotics, including codeine. Therefore, an appropriate dose of naloxone hydrochloride should be administered, preferably by the intravenous route and simultaneously with efforts at respiratory resuscitation. Since the duration of action of dihydrocodeine may exceed that of the antagonist, the patient should be kept under continued surveillance and repeated doses of the antagonist should be administered as needed to maintain adequate respiration.

An antagonist should not be administered in the absence of clinically significant respiratory or cardiovascular depression.

Oxygen, intravenous fluids, vasopressors, and other supportive measures should be employed as indicated.

Gastric emptying may be useful in removing unabsorbed drug.

Acetaminophen: Signs and Symptoms: In acute acetaminophen overdosage, dose-dependent, potentially fatal hepatic necrosis is the most serious adverse effect. Renal tubular necrosis, hypoglycemic coma, and thrombocytopenia may also occur. In adults, hepatic toxicity has rarely been reported with acute overdoses of less than 10 grams and fatalities with less than 15 grams. Importantly, young children seem to be more resistant than adults to the hepatotoxic effect of an acetaminophen overdose. Despite this, the measures outlined below should be initiated in any adult or child suspected of having ingested an acetaminophen overdose.

Early symptoms following a potentially hepatotoxic overdose may include: nausea, vomiting, diaphoresis, and general malaise. Clinical and laboratory evidence of hepatic toxicity may not be apparent until 48 to 72 hours post-ingestion.

Treatment: The stomach should be emptied promptly by lavage or by induction of emesis with syrup of ipecac. Patients' estimates of the quantity of a drug ingested are notoriously unreliable. Therefore, if an acetaminophen overdose is suspected, a serum acetaminophen assay should be obtained as early as possible, but no sooner than four hours following ingestion. Liver function studies should be obtained initially and repeated at 24-hour intervals.

The antidote, N-acetylcysteine, should be administered as early as possible, preferably within 16 hours of the overdose ingestion for optimal results, but in any case within 24 hours. Following recovery, there are no residual, structural or functional hepatic abnormalities.

DOSAGE AND ADMINISTRATION: Dosage should be adjusted according to the severity of the pain and the response of the patient. DHC Plus™ is given orally. The usual adult dosage is two capsules every (4) hours as needed for pain.

CAUTION: Federal law prohibits dispensing without prescription.

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acetaminophen 356.4 mg
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CONTACT INFORMATION

UNM SOM—University of New Mexico School of Medicine, Office of CME, PO Box 713, Albuquerque 87131. (505) 277-3942.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. Accredited institutions wishing to list AMA Category 1 CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, UT 84102; or phone (801) 355-5290. For information on CME accreditation, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution.

September 22-25—**Utah Medical Association Annual Meeting.** University Park Hotel, Salt Lake City. Wed-Sat. Contact: UMA, 540 E Fifth South, Salt Lake City 84102. (801) 355-7477.

MEDICAL GRAND ROUNDS

Weekly—Internal Medicine Grand Rounds, Psychiatry Grand Rounds, OB/GYN Grand Rounds, Pediatric Grand Rounds. Contact: UUSM, Office of CME, (801) 581-8664.

SPONSORS OF COURSES—ABBREVIATIONS

CH:	Castleview Hospital, 300 N Hospital Dr, Price 84501. (801) 637-4800.
CS:	Charter Summit Hospital, 175 W 7200 South, Midvale 84047. (801) 561-8181.
DM:	Dixie Medical Center, 544 S 400 East, St George 84770. (801) 634-4000.
ETS:	Emergency Training Services, 777 N 390 East, American Fork 84003. (801) 763-3555.
FHP:	FHP of Utah, 35 W Broadway, Salt Lake City 84101. (801) 355-1234.
ITS:	Intermountain Thoracic Society, 1616 S 11th East, Salt Lake City 84105. (801) 484-4456.
LDSH:	LDS Hospital, 8th Ave and "C" St, Salt Lake City 84143. (801) 321-1100.
LRH:	Logan Regional Hospital, 1400 N 5th East, Logan 84321. (801) 752-2050.
MVH:	Mountain View Hospital, 1000 E Highway 6, Payson 84651. (801) 465-9201.
OSS:	Ogden Surgical-Medical Society, PO Box 9311, Ogden 84409.
PCMC:	Primary Children's Medical Center, 100 N Medical Dr, Salt Lake City 84113. (801) 588-2000.
PVH:	Pioneer Valley Hospital, 3460 S 4155 West, West Valley City 84120. (801) 968-9061.
UMIA:	Utah Medical Insurance Association, 540 E 500 South, Salt Lake City 84102. (801) 531-0375.
UOS:	Utah Ophthalmological Society, 540 E 500 South, Salt Lake City 84102. (801) 355-7477.
USH:	Utah State Hospital, PO Box 270, Provo 84603-0270. (801) 373-4400.
UUSM	University of Utah School of Medicine, Office of Continuing Medical Education, 50 N Medical Dr, Salt Lake City 84132. (801) 581-8664.
VAMC:	Veterans Administration Medical Center, 500 Foothill Dr, Salt Lake City 84148. (801) 582-1565.

WASHINGTON

The listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here, please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 1100, Seattle, WA 98121; or phone (206) 441-9762 or (800) 552-0612.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

August 15-18—**Oncology.** Everett. Sun-Wed. Contact: PNMEII. (206) 258-6322.

August 27-28—**Children's Orthopedic Conference.** Seattle. Fri-Sat. Contact: Children's Hospital, (206) 526-2501.

September 9-12—**Washington State Medical Association Annual Meeting and Scientific Session.** Jantzen Beach, Oregon. Thurs-Sun. Contact: WSMA.

September 10—**Emergency Physicians Scientific Session.** Jantzen Beach. Fri. Contact: WACEP, (206) 441-9762.

September 11—**Ophthalmology Scientific Session.** Jantzen Beach. Sat. Contact: WAEPS, (206) 441-9762.

September 13-17—**21st Annual Advances in Family Practice.** Seattle. Mon-Fri. Contact: U/W.

September 17—**Family Practice Day.** Renton. Fri. Contact: Valley Medical Center, (206) 228-3440.

September 17-18—**Children's Orthopedic Conference.** Seattle. Fri-Sat. Contact: Children's Hospital. (206) 526-2501.

September 22-25—**North Pacific Pediatric Society.** Vancouver, BC. Wed-Sat. Contact: Children's. (206) 258-6322.

September 23—**Domestic Violence.** Everett. Thurs. Contact: PNMEII, (206) 258-6322.

September 24-25—**Diabetes Update.** Seattle. Fri-Sat. Contact: U/W.

September 30-October 1—**Atherosclerosis and Restenosis.** Seattle. Thurs-Fri. Contact: U/W.

October 1—**Pharmacology.** Tacoma. Fri. Contact: Multicare, (206) 522-1221.

October 8-9—**Society for Pediatric Pathology.** Seattle. Wed-Fri. Contact: Children's Hospital, (206) 526-2501.

October 8-9—**Upper Respiratory Infection.** Seattle. Fri-Sat. Contact: U/W.

October 15—**The Walking Wounded—Acute Care Outside the ICU.** Everett. Fri. Contact: PNMEII, (206) 258-6322.

October 20—**Perinatology Day.** Tacoma. Wed. Contact: Multicare, (206) 522-1221.

October 22-23—**Adolescent Medicine.** Seattle. Thurs-Fri. Contact: Children's Hospital, (206) 526-2501.

October 23—**Pediatric Endocrinology.** Tacoma. Fri. Contact: Multicare, (206) 522-1221.

October 27—**Perinatology Conference.** Tacoma. Wed. Contact: Multicare, (206) 552-1221.

November 4-5—**Drug Therapy.** Seattle. Thurs-Fri. Contact: U/W.

November 18-19—**Regional Musculoskeletal Conference.** Seattle. Thurs-Fri. Contact: U/W.

November 19—**Advances in Therapeutics for the Clinician.** Renton. Fri. Contact: VMC, (206) 228-3440.

December 2-4—**American College of Physicians.** Seattle. Thurs-Sat. Contact: U/W.

December 9-12—**9th Infectious Disease Conference.** Everett. Tues-Sat. Contact: PNMEII, (206) 258-6322.

December 10-11—**Regional Musculoskeletal Conference.** Seattle. Fri-Sat. Contact: U/W.

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104. (206) 223-5953.

PCMS CME—Contact: Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 223-6898.

WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Suite 900, Seattle, WA 98121. (206) 441-9762.

WYOMING

October 29-30—**16th Annual Perinatal Conference.** Children's Hospital of Denver at Laramie. Fri-Sat. Contact: Conference Office, (303) 861-6946 or (800) 225-0010. ◆

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California Department of Health Services
Kaiser Family Foundation
Levi Strauss Foundation
National Association of Counties
National Association of Public Hospitals
National Association of Social Workers
National Hospice Organization
National Minority AIDS Council
San Francisco Department of Public Health
San Francisco Medical Society
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- pharmacists
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- mental health practitioners
- dentists
- social workers
- program administrators
- government and community leaders
- community-based and HIV/AIDS service organizations, administrators and caregivers
- hospital service and planning managers

Plenary and workshop sessions reflecting various levels of attendee knowledge and expertise bring attention to HIV/AIDS issues in five Conference tracks:

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- **Treatment**
- **Health Services/Program Evaluation**

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- Emphasize emerging issues related to specific populations, including minorities, women, children, homeless, adolescents, intravenous drug users, the elderly, and the differently-abled
- Examine issues pertaining to access and affordable health care
- Discuss issues related to integrating or mainstreaming HIV care and services
- Examine issues related to health care reform
- Present research related to program evaluation

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For general information, to register or exhibit, contact:

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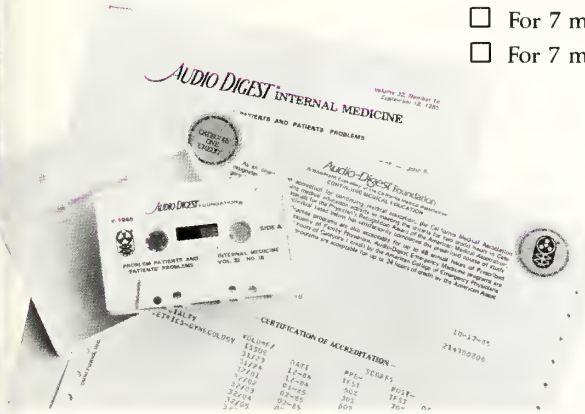

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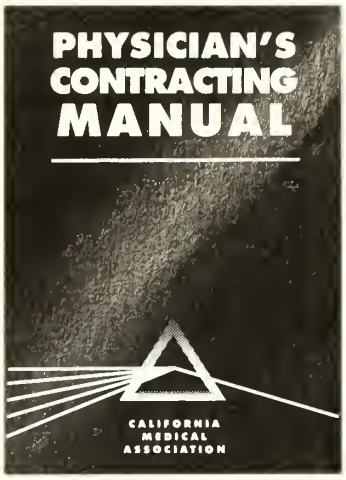

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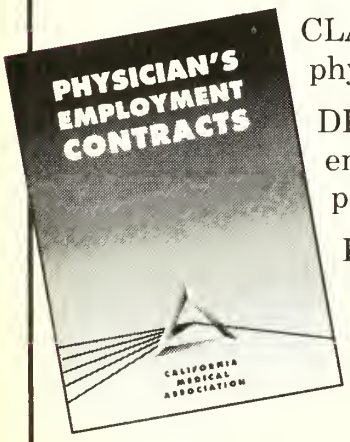

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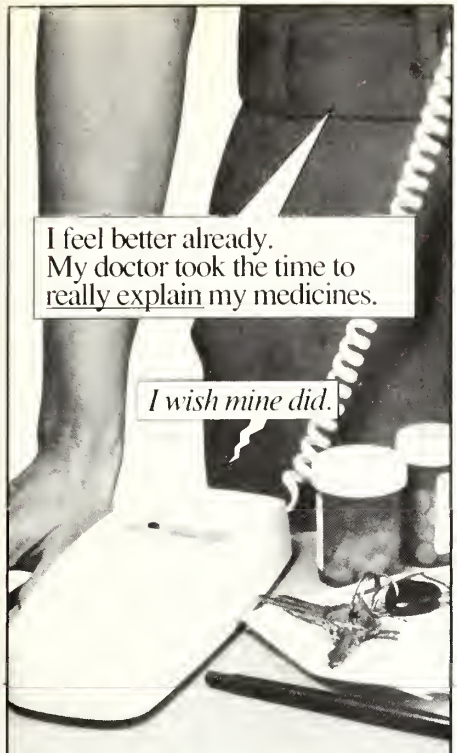

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Indications and Usage: *Augmentin* is indicated in the treatment of infections caused by susceptible strains of the designated organisms in the conditions listed below.

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Otitis Media caused by β-lactamase-producing strains of *Hemophilus influenzae* and *Moraxella (Branhamella) catarrhalis*

Sinusitis caused by β-lactamase-producing strains of *Hemophilus influenzae* and *Moraxella (Branhamella) catarrhalis*

Skin and Skin Structure Infections caused by β-lactamase-producing strains of *Staphylococcus aureus*, *E. coli*, and *Klebsiella* spp.

Urinary Tract Infections caused by β-lactamase-producing strains of *E. coli*, *Klebsiella* spp. and *Enterobacter* spp.

While *Augmentin* is indicated only for the conditions listed above, infections caused by ampicillin-susceptible organisms are also amenable to *Augmentin* treatment due to its amoxicillin content. Therefore, mixed infections caused by ampicillin-susceptible organisms and β-lactamase-producing organisms susceptible to *Augmentin* should not require the addition of another antibiotic.

Bacteriological studies, to determine the causative organisms and their susceptibility to *Augmentin*, should be performed together with any indicated surgical procedures.

Therapy may be instituted prior to obtaining the results from bacteriological and susceptibility studies to determine the causative organisms and their susceptibility to *Augmentin* when there is reason to believe the infection may involve any of the β-lactamase-producing organisms listed above. Once the results are known, therapy should be adjusted, if appropriate.

Contraindications: A history of allergic reactions to any penicillin is a contraindication.

WARNINGS: SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTOID) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY. ALTHOUGH ANAPHYLAXIS IS MORE FREQUENT FOLLOWING PARENTERAL THERAPY, IT HAS OCCURRED IN PATIENTS ON ORAL PENICILLINS. THESE REACTIONS ARE MORE LIKELY TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR A HISTORY OF SENSITIVITY TO MULTIPLE ALLERGENS. THERE HAVE BEEN REPORTS OF INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS. BEFORE INITIATING THERAPY WITH ANY PENICILLIN, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS OR OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, *AUGMENTIN* SHOULD BE DISCONTINUED AND THE APPROPRIATE THERAPY INSTITUTED. **SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE, OXYGEN, INTRAVENOUS STEROIDS AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.**

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including *Augmentin*, and has ranged in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of "antibiotic associated colitis."

Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation and treatment with an antibacterial drug clinically effective against *C. difficile* colitis.

Precautions: General: While *Augmentin* possesses the characteristic low toxicity of the penicillin group of antibiotics, periodic assessment of organ system functions, including renal, hepatic and hematopoietic function, is advisable during prolonged therapy.

A high percentage of patients with mononucleosis who received ampicillin develop a skin rash. Thus, ampicillin class antibiotics should not be administered to patients with mononucleosis.

The possibility of superinfections with mycotic or bacterial pathogens should be kept in mind during therapy. If superinfections occur (usually involving *Pseudomonas* or *Candida*), the drug should be discontinued and/or appropriate therapy instituted.

Drug Interactions: Probenecid decreases the renal tubular secretion of amoxicillin. Concurrent use with *Augmentin* may result in increased and prolonged blood levels of amoxicillin.

The concurrent administration of allopurinol and ampicillin increases substantially the incidence of rashes in patients receiving both drugs as compared to patients receiving ampicillin alone. It is not known whether this potentiation of ampicillin rashes is due to allopurinol or the hyperuricemia present in these patients. There are no data with *Augmentin* and allopurinol administered concurrently.

Augmentin should not be co-administered with Antabuse® (disulfiram).

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate carcinogenic or mutagenic potential.

Pregnancy (Category B): Reproduction studies have been performed in mice and rats at doses up to ten (10) times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to *Augmentin*. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery: Oral ampicillin class antibiotics are generally poorly absorbed during labor. Studies in guinea pigs have shown that intravenous administration of ampicillin decreased the uterine tone, frequency of contractions, height of contractions and duration of contractions. However, it is not known whether the use of *Augmentin* in humans during labor or delivery has immediate or delayed adverse effects on the fetus, prolongs the duration of labor or increases the likelihood that forceps delivery or other obstetrical intervention or resuscitation of the newborn will be necessary.

Nursing Mothers: Ampicillin class antibiotics are excreted in the milk; therefore, caution should be exercised when *Augmentin* is administered to a nursing woman.

Adverse Reactions: *Augmentin* is generally well tolerated. The majority of side effects observed in clinical trials were of a mild and transient nature and less than 3% of patients discontinued therapy because of drug-related side effects. The most frequently reported adverse effects were diarrhea/loose stools (9%), nausea (3%), skin rashes and urticaria (3%), vomiting (1%) and vaginitis (1%).

The overall incidence of side effects, and in particular diarrhea, increased with the higher recommended dose. Other less frequently reported reactions include: abdominal discomfort, flatulence and headache.

The following adverse reactions have been reported for ampicillin class antibiotics:

Gastrointestinal: Diarrhea, nausea, vomiting, indigestion, gastritis, stomatitis, glossitis, black "hairy" tongue, enterocolitis and pseudomembranous colitis. Onset of pseudomembranous colitis symptoms may occur during or after antibiotic treatment (see WARNINGS).

Hypersensitivity reactions: Skin rashes, urticaria, angioedema, serum sickness like reactions (urticaria or skin rash accompanied by arthritis/arthralgia, myalgia, and frequently fever), erythema multiforme (rarely Stevens-Johnson Syndrome), and an occasional case of exfoliative dermatitis have been reported. These reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids. Whenever such reactions occur, the drug should be discontinued, unless the opinion of the physician dictates otherwise. Serious and occasional fatal hypersensitivity (anaphylactic) reactions can occur with oral penicillin (see WARNINGS).

Liver: A moderate rise in AST (SGOT) and/or ALT (SGPT) has been noted in patients treated with ampicillin class antibiotics but the significance of these findings is unknown. Hepatic dysfunction, including increases in serum transaminases (AST and/or ALT), serum bilirubin and/or alkaline phosphatase, has been infrequently reported with *Augmentin*. The histologic findings on liver biopsy have consisted of predominantly cholestatic, hepatocellular or mixed cholestatic-hepatocellular changes. The onset of signs/symptoms of hepatic dysfunction may occur during or after therapy. Complete resolution has occurred with time.

Hemic and Lymphatic Systems: Anemia, thrombocytopenia, thrombocytopenic purpura, eosinophilia, leukopenia and agranulocytosis have been reported during therapy with penicillins. These reactions are usually reversible on discontinuation of therapy and are believed to be hypersensitivity phenomena. A slight thrombocytosis was noted in less than 1% of the patients treated with *Augmentin*.

Central Nervous System: Reversible hyperactivity, agitation, anxiety, insomnia, confusion, behavioral changes, and/or dizziness have been reported rarely.

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† Latest available annual data: January to December 1991.

‡ *In vitro* susceptibility does not necessarily imply *in vivo* efficacy.

Please see brief summary of prescribing information for contraindications, warnings, precautions and adverse reactions on adjacent page.

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Articles

Acute Injuries From Mountain Biking

TONY K. CHOW, MD, *Loma Linda;* MARK D. BRACKER, MD, *and* KEVIN PATRICK, MD, MS, *La Jolla, California*

We questioned members of 2 southern California off-road bicycling organizations about injuries associated with the use of all-terrain bicycles. Cyclists were asked about riding and safety habits, the kind(s) of injury sustained with their most recent accident and whether they sought medical treatment, and the circumstances of the accident. Of 459 mailed surveys, 268 (58.4%) were returned. Respondents (82.8% of whom were male) ranged in age from 14 to 68 years. Of these, 225 (84%) had been injured while riding all-terrain bicycles, 51% in the past year. Although most injuries were characterized as minor, 26% required professional medical care, and 4.4% of those injured were admitted to hospital. Extremity injuries—abrasions, lacerations, contusions—occurred in 201 (90%) cyclists with 27 (12%) sustaining a fracture or dislocation. High levels of helmet use (88%) may explain the low occurrence of head and neck trauma (12%). Frequent riding and riding on paved terrain were associated with increased severity of injury, although most accidents—197 (87.6%)—occurred off paved roads. These results suggest that, compared with regular bicyclists, all-terrain cyclists have more, but not necessarily more severe, injuries. Clinicians and emergency medical personnel should be aware that the increasing popularity of off-road cycling may change the frequency and nature of bicycling injuries.

(Chow TK, Bracker MD, Patrick K: Acute injuries from mountain biking. West J Med 1993; 159:145-148)

As recreational bicycling changes, we can expect to see a change in injuries to cyclists. According to industry statistics, the most widely sold bicycle is now the all-terrain bicycle (ATB) or "mountain bike," accounting for an estimated 67% of sales in 1990.[1] An ATB is a 10- to 21-speed bicycle with a heavy-duty frame, relatively upright riding geometry, special brakes and components, and "fat" tires designed to allow the rider to travel on various types of terrain, including dirt roads, gravel, and "single-track" paths. We describe the frequency, type, and severity of injuries sustained in mountain bike accidents and try to clarify the circumstances and risk factors leading to their occurrence.

Previous studies of bicycling injuries have focused on children,[2,3] urban settings,[4,5] head injuries,[3,6-8] and helmet use.[9-11] Most have looked at injuries from the standpoint of riders who required medical attention,[5,7,12,13] autopsies,[6,14] or both, limiting discussion to only the most seriously injured and neglecting the rest of those who participate in the sport. We know of no reports that detail the injuries sustained in the comparatively new pastime of mountain biking. Thus we chose to investigate retrospectively mountain bicyclists who generally ride off road, concentrating on acute injuries whether or not they received medical treatment.

Methods

We mailed an anonymous two-page questionnaire to each of the 252 members of a Los Angeles bicycling club and to the 207 members of a similar San Diego club. Both clubs specifically encourage off-road recreational cycling. As an incentive to respond, we included an offer to win, by lottery, one of four gift certificates from a bicycle shop. At one-month intervals for two months, we sent reminders to those who did not respond.

After requesting demographic information, the questionnaire contained multiple-choice questions about riders' experience, equipment use, and bicycle maintenance habits. Cyclists who had ever been injured were asked about their most recent injury. We defined an injury as "the presence of pain, discomfort, or disability," rated as mild if no treatment was needed or if it was self-treated, moderate if medical care was sought, and severe if admission to a hospital was required. We requested details of the accident leading to the injury, including the nature of the ride; the type and grade of the terrain, weather characteristics, whether a collision occurred; if equipment had failed; helmet use at the time of accident; alcohol or drug use; and contributing factors such as excessive speed, inattentiveness, unfamiliarity with terrain, and poor riding ability.

We used the computer programs EXCEL and STATVIEW to organize and tabulate the data. All riders who reported injuries were divided into two groups—those who sought professional medical attention (moderate and severe injuries) and those who did not (mild). We then compared the details of the accidents between these two groups to identify risk factors for serious injuries. The

From the Department of Emergency Medicine, Loma Linda University Medical Center (Dr Chow); the Department of Community and Family Medicine, University of California, San Diego, School of Medicine (Drs Bracker and Patrick); and the Student Health Services, San Diego State University (Dr Patrick).

This work was supported in part by a grant from the San Diego State University Student Health Center and from the Bicycle Coalition of San Diego.

Reprint requests to Tony K. Chow, MD, House Staff Office, Loma Linda University Medical Center, 11234 Anderson St, Loma Linda, CA 92354.

TABLE 1.—*Demographics and Mountain Bike Use Among 268 Off-road Riders, Southern California, 1990*

Demographics	*Value*
Age, yr (SD)	
Mean	36.2 (±9.4)
Median	36
Range	14 to 68
Sex, No. (%)	
Male	222 (82.8)
Female	46 (17.2)
Years riding, No. (SD)	
Mean	4.2 (±2.3)
Range	0.33 to 15
Frequency of riding/× wk, %	
<1	10.1
1-2	44.4
3-5	41.4
≥6	4.1
Total hr/wk (SD)	
Mean	6.6 (±3.9)
Range	0.5 to 28
Off-road hr/wk (SD)	
Mean	5.0 (±3.1)
Range	0 to 20

Student's *t* test was used and χ^2 analysis with Yates's correction applied where appropriate for 2 × 2 contingency tables.*

Results

Of the 459 surveys sent, 268 were returned, yielding a response rate of 58.4%—59.5% from Los Angeles, 57.0% from San Diego. Those who returned the questionnaire will be referred to as "riders." The demographic results are shown in Table 1. The age of the riders ranged from 14 to 68. Most riders were male (82.8%), which corresponds to the proportion of males and females in the study population (club members), estimated from the original mailing lists. The mean number of years' experience on a mountain bike was 4.2 (SD 2.3) with responses ranging from 4 months to 15 years. On average, riders indicated a mean of riding 6.6 hours total on their mountain bikes each week, and of this, 5 hours per week (76%) were spent riding off road. Thus, this group fulfilled the criteria of being predominantly off-road riders.

Injuries

Of the 268 riders, 225 (84%) reported sustaining at least one injury while all-terrain bicycling (Table 2). Of all riders, 137 (51.1%) were injured in the past year. We cannot estimate the actual incidence of injury because cyclists may have been involved in more than one accident in the preceding year. Almost 90% of the injured riders (n = 201) damaged extremities. In all, 37% (n = 84) sustained an injury or injuries to the trunk, and head and neck trauma occurred in 12% (n = 27) of victims. Most injuries were mild, requiring no treatment (21.8%), or were self-treated (48%). A quarter (26%) of the victims saw physicians either in an emergency department (14.6%) or in the office. Ten cyclists (4.4%) were admitted to hospital, generally for less than a week, but one was an inpatient for 30 days.

Circumstances of Accidents Leading to Injury

Most injury-causing accidents occurred during the months of June and July and the fewest in the winter months. Injuries happened predominantly during the middle of the day (63.1%) in clear weather (89.3%) while the victim was riding primarily for recreation (86.7%). Injuries were more likely to occur off road (87.6%) than on paved terrain (Table 3), and most happened while descending a grade (74.2%). Most of the injured fell without a preceding collision. In 23 collisions leading to injury, 13 were with stationary objects. The other 10 collisions were with a moving object, either another bicycle or a motor vehicle. Of the five incidents involving a motor vehicle, four occurred on paved terrain, with all five sustaining injuries severe enough to cause the riders to miss school or work; all but one required professional medical attention.

*Deborah Wingard, PhD, assisted with the development of the survey and with statistical analysis. David Asada collected data and helped organize it.

TABLE 2.—*Characteristics of Injuries Among 225 Off-road Victims in Their Most Recent Mishap, Southern California, 1990*

Anatomic Location	*Injury*	*Victims, No.**	*Percentage of All Victims, n=225†*
Extremities	Laceration, abrasion	167	74.2
	Contusion	76	33.8
	Sprain, strain	30	13.3
	Fracture, dislocation	27	12.0
Trunk	Laceration, abrasion	49	21.8
	Contusion	41	18.2
	Internal injury	13	5.8
Head, neck	Laceration, abrasion	25	11.1
	Contusion	8	3.6
	Fracture	1	0.4

*225 victims sustained 437 injuries.
†The sum of totals equals more than 100% because each victim may have had more than 1 injury for each anatomic location.

TABLE 3.—*Characteristics of the Most Recent Ride in Which Injury Occurred Among 225 Off-road Victims, Southern California, 1990*

Characteristic	Injury Victims, n=225 No.*	%
Type of terrain		
Paved	28	12.4
Dirt	96	42.7
Rocks	29	12.9
Sand	4	1.8
Combination of dirt, rocks, sand	60	26.7
Other	8	3.6
Grade		
Steep uphill	8	3.6
Moderate uphill	12	5.3
Flat	34	15.1
Moderate downhill	90	40.0
Steep downhill	77	34.2

*Totals do not equal 225 for all characteristics because not all responded.

Of those injured, 80 (36%) thought excessive speed contributed to their mishap; 78 (34.7%) attributed it to riding unfamiliar terrain. Other factors included inattentiveness (22.7%) and riding beyond their ability (19.6%). Six of the injured (2.6%) reported that they were using either alcohol or marijuana at the time of the accident. Many (20%) could not continue with their intended ride after the accident mainly because their injuries were too severe. Among those, 17 said they walked away from the injury site, but 10 of them needed to be carried from the scene, 1 by helicopter.

Safety Practices and Equipment Failure

Of the 268 riders, more than half (55%) provided maintenance for their bikes six times a year or more. Most (86%) wore helmets routinely; only 2.2% stated they never used a helmet. At the time of their accident 88% (n = 198) were wearing a helmet. Equipment failure caused 7% of the accidents. The most common items that failed were the brakes and tires. Other equipment lapses involved the front fork, handle bar, and headset.

Risk Factors for Severe Injuries

We compared those who sustained injury requiring professional medical attention with those who had had accidents but received only mild injuries. The two groups did not differ significantly in age, sex, and years of experience on an all-terrain bicycle. The more seriously injured group tended to ride more total hours each week (7.8 versus 6.3, $P < .01$) and more off-road hours each week (5.7 versus 4.8, $P < .05$). When the circumstances of their accident were compared, the group that required a physician's evaluation were more likely to have had their mishap while riding on paved terrain than off road ($P < .01$).

Discussion

Mountain biking resulted in injuries to 84% of the members of two southern California ATB cycling clubs who responded to our survey. Although most were minor extremity injuries requiring only self-care, a quarter required medical attention and 5% admission to hospital. Given the growing popularity of ATB ownership, which soared from 200,000 in 1983 to 11 million in 1989,[15] it is apparent that accidents from mountain biking are common. By describing these injuries and the circumstances in which they occurred, we have tried to clarify risk factors and to aid in accident prevention and treatment.

Most ATB riders in this study injured themselves while cycling off road downhill. Important contributing factors included excessive speed, unfamiliar terrain, and inattentive riding. Equipment failure played a role, but less often than the 10% to 15% found among road riding accidents.[16,17]

We are confident that the respondents are representative of the entire study group, first, because our response rate compares favorably with rates in other mailed surveys, and, second, because those who replied have demographic characteristics similar to those members who did not reply.

Nevertheless, we urge caution in interpreting the results for several reasons. Injured club members may be more motivated to respond, although as other retrospective studies have the same weakness, comparisons are valid. We obviously missed any deceased riders and possibly any who stopped mountain bike riding because of severe injuries. In both situations, the results may underestimate the true risk. Respondent recall could also lead to biased results, particularly when a subjective judgment is called for. This seems less of a problem for objective detail such as injury type, severity, anatomic location, and treatment method.

Other studies using similar methods have found that road conditions contribute to as much as 52% of bicycle accidents.[16] Because most off-road mountain biking occurs on irregular terrain, accidents would be expected to be common. In fact, nearly 83% of mountain bike racers in Mammoth Mountain had had accidents, resulting in an average of 8.5 accidents per person (T.K.C., unpublished data, September 1989).

We compared our results with three other survey-based studies of bicycling injuries (Table 4). Kruse and McBeath randomly surveyed 539 college student cyclists in Wisconsin: 29% had been in an accident within the previous three years; a third of those required professional medical attention.[16] Sgaglione and colleagues polled 93 urban cyclists at Manhattan bicycle meets.[4] Half had had at least one accident leading to injury, 37% of which required medical care. An investigation similar to ours was done on 492 members of two Kansas City bicycling clubs who were principally recreational riders on paved terrain. Nearly half (46.3%) had had an accident leading to trauma.[17] Of those injured, 34.8% needed medical attention or were admitted to hospital. Thus, although

TABLE 4.—*Review of Retrospective Surveys of Biking Injuries*

Study and Location	*Cyclists, No.*	*Mean Age, yr*	*Cyclists Reporting Injuries, %*	*Injured Victims Seeking Medical Care, %*	*Injured Victims Admitted to Hospital, %*
Kruse and McBeath, 1980[16] Madison, Wisconsin	539	23	18.0*	32.0	1
Sgaglione et al, 1982[4] Manhattan, New York	93	25	50.4†	31.0	6
Kiburz et al, 1986[17] Kansas City, Missouri	492	34	46.3	23.8	11
This study, 1990 Southern California	268	36	84.0	26.0	4.4

*29% of the bicyclists had an accident in the previous 3 years, of which 62% were injured.
†54.8% of the bicyclists had an accident of which 92% were injured.

our results suggest that the incidence of injuries from mountain biking is higher than that from road cycling, the proportion of injuries requiring a physician's evaluation is comparable.

In contrast to other studies, we found a low occurrence of head injuries and a high use of safety helmets (90%). This offers further support to Thompson and coworkers, who demonstrated the effectiveness of helmets in preventing serious head injury.[10] Although it is known that children wear helmets infrequently[3,9,11] and that their use increases with age,[9,10] the best documented compliance rate for all ages is still no better than 57%.[8] What accounts for the apparent willingness of the ATB riders we studied to wear helmets? Because they are older they may not only be more aware of studies advocating their use[18] and more able to afford them, but may also be less likely than younger cyclists to think that helmets are "uncool."[3] Rules of the National Off-Road Bicycling Association requiring helmet use in all their racing events may influence those members of the club who ride competitively. Last, mountain bikers may know that they run a high risk of injury. This would support data from University of New Mexico (Albuquerque) students suggesting that perceived risk is an important factor in the use of safety helmets.[19]

With this information, health care professionals can better educate ATB riders about injuries typical of the sport and their risk factors. Clinicians should reinforce helmet use and equipment maintenance and encourage cyclists who ride on paved roads to be particularly aware of motor vehicles and follow traffic regulations. Advising frequent riders that they run a higher risk of injury might increase their level of caution. For ATB riders who ride off road, appropriate speed—particularly downhill—is critical. Learning the terrain they plan to travel, perhaps with someone familiar with the area, might also be helpful.

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Articles

Prevention of Cesarean Section
Does Intracervical Dinoprostone Work?

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We investigated the effect of preinduction cervical ripening with the intracervical instillation of dinoprostone (prostaglandin E_2 gel, 0.5 mg) on the results of labor induced with intravenous oxytocin. We randomly allocated 79 pregnant women to receive either the intracervical application of dinoprostone gel or placebo gel. Compared with control subjects, the group who received dinoprostone had no difference in induction-to-delivery interval or in cesarean section rate. The dinoprostone group had fewer failed inductions, but there was no difference between the two groups in the number who delivered spontaneously within 24 hours. From review of the literature and a meta-analysis, it was likewise revealed that dinoprostone did not favorably affect the cesarean section rate. Contrary to current opinion, intracervical dinoprostone gel does not appreciably lower the cesarean section rate when used at this dose and route before labor is induced.

(Gilson GJ, Izquierdo LA, Chatterjee MS, Curet LB, Qualls CR: Prevention of cesarean section—Does intracervical dinoprostone work? West J Med 1993; 159:149-152)

Both maternal and fetal complications of pregnancy often require the induction of labor before spontaneous labor. These complications frequently occur before cervical ripening, resulting in failed induction and delivery by cesarean section. In the past decade, concern has grown over the sharp escalation in the rate of cesarean delivery, and inductions that result in a "failure to progress" are an important contributor to this rise.

The local application of prostaglandin E_2 (PGE_2) produces changes in the cervical collagen ground substance that make the cervix more distensible and responsive to uterine contractions.[1,2] Numerous reports have documented the beneficial effects of various prostanoids on the results of labor. These reports, while showing changes in the cervical Bishop score as a result of prostaglandin application, do not uniformly demonstrate a reduced number of failed inductions or a reduced incidence of cesarean delivery.[3,4] Likewise, some of the studies showing benefit were not placebo controlled, making the interpretation of efficacy problematic. Disconcerted by our own rate of cesarean section of 48% in induced patients with unfavorable eervices versus our 14% overall cesarean rate, we undertook the current study to determine whether the intracervical application of dinoprostone gel, 0.5 mg, could be of benefit in lowering the cesarean section rate in this group of high-risk pregnant women at term.

Patients and Methods

Women admitted to the University of New Mexico Hospital (Albuquerque) for the induction of labor were included in this prospective, randomized, double-blind study. Of 100 women whose medical records were reviewed, 79 met strict protocol criteria and were evaluable. Only women with single pregnancies, intact membranes, no evidence of fetal compromise, and who had a Bishop score of 4 or less were entered into the study. Patients with a history of asthma, glaucoma, ruptured membranes, breech presentation, or abnormal vaginal bleeding were excluded, as were patients with two or more previous cesarean sections. The study protocol was approved by the Human Research Review Committee of the University of New Mexico Hospital, and all patients gave written informed consent. Patients were randomly assigned to either the drug (n = 41) or placebo (n = 38) group; the assignment was blinded to both physician and patient, the randomization having been carried out in the pharmacy.

Once a decision was made to induce labor, the patient underwent a cervical examination, and a Bishop score was determined.[5] If the score was 4 or lower, the cervix was considered unfavorable and the patient was admitted to the study. Patients in the drug group had 0.5 mg of dinoprostone (Prostin E2, Upjohn) dissolved in 3 ml of sterile methylcellulose gel inserted into the upper endo-

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TABLE 1.—*Patient Profile for Intracervical Dinoprostone Gel Study*

Patient Characteristics	Study Group: Dinoprostone, n=41	Study Group: Control, n=38	P
Maternal age, yr ± SD	26.9 ± 5.6	25.5 ± 5.9	.86
Nullipara, No. (%)	19 (46)	14 (37)	.49
Previous cesarean section, No. (%)	3 (7)	1 (2.6)	.62
Gestational age, wk ± SD	38.7 ± 2.9	39.4 ± 2.5	.86
Preterm (<37 wk, No. (%)	6 (15)	4 (10.5)	.74
Indication for induction, No. (%)			
Hypertensive disease	22 (54)	16 (42)	.37
Past due date	10 (24)	12 (32)	.62
Intrauterine growth retardation	3 (7)	2 (5)	1.00
Diabetes mellitus	2 (5)	4 (10.5)	.42
Other medical conditions	4 (10)	4 (10.5)	1.00

cervical canal by means of a 2.5-mm Portex infant endotracheal tube, with care taken that an excessive quantity of gel did not spill into the posterior vaginal fornix. Patients in the control group underwent similar instillation of the placebo, which was made by mixing starch with methylcellulose gel until opacity was matched so that both investigators and patients were blinded. Complete details of the method of gel preparation have been previously reported.[6] Electronic fetal monitoring was carried out for an hour after gel instillation, whereupon the patient was allowed to rest overnight. Twelve hours after the gel had been placed, the cervical Bishop score was reassessed by the same examiner, and oxytocin induction was begun. Amniotomy was done when the patient was in active labor and cervical dilation allowed it. Induction was considered a failure if persistent uterine activity of 200 Montevideo units, accompanied by cervical change, was not achieved despite the patient having received oxytocin according to a strict protocol over a 12-hour period.[7] If maternal and fetal surveillance was reassuring, as they were in most of these patients, the patient was rested overnight and oxytocin was readministered the following day. The induction was considered a failure, however, because the patient had not delivered in the first 24-hour period. Patients were managed by resident physicians following this protocol under our direct supervision. The oxytocin infusion rate was not allowed to exceed 20 milliunits per minute.

Statistical analysis of the two groups was carried out using the two-tailed *t* test for continuous data and χ^2 or Fisher's exact test for the frequency data where appropriate. Ordinal data were analyzed using the Wilcoxon ranked sums test. A power study revealed that 39 subjects would be required in each group to detect a reduction in the cesarean section rate from 45% to 15% with a 90% power and using an α of .05. Using the Mantel-Haenszel statistic, meta-analysis was done on information combined from previous studies.

Results

The indications for inducing labor and other characteristics of the two groups are summarized in Table 1; there were no significant differences between the two groups. Table 2 summarizes the results of the two study groups. As can be seen, there was a significant difference in the incidence of delivery by cesarean section in the

TABLE 2.—*Outcome of Cervical Ripening, Labor, and Delivery*

Outcome Variable	Study Group: Dinoprostone, n=41	Study Group: Control, n=38	P
Initial Bishop score ± SD	2.6 ± 0.2	2.7 ± 0.2	.79
12-Hr Bishop score ± SD	4.3 + 0.3	4.5 + 0.3	.79
Change in Bishop score ± SD	1.7 ± 0.2*	1.7 ± 0.2*	.76
Gel-instillation interval, hr ± SD	25.9 ± 1.65	24.2 ± 1.60	.47
Oxytocin-administration time, hr ± SD	16.4 ± 1.56	13.4 ± 1.46	.16
Spontaneous labor after gel (%)	2 (4.8)	1 (2.6)	.60
Deliveries, No. (%)			
Failed inductions	3 (7)	11 (29)	.02†
Vaginal delivery	22 (54)	21 (55)	.89
Cesarean section	16 (39)	6 (16)	.02‡
Infant weight, grams ± SD	3,098 ± 120	3,264 ± 101	.30
Apgar score at 5 min ± SD	8.61 ± 0.13	8.65 ± 0.14	.85

*Differences between initial and 12-hour Bishop scores show a significant increase ($P < .001$) for both groups.
†Relative risk for failed induction after dinoprostone use = 0.25 (95% confidence interval [CI] = 0.09, 0.74).
‡Relative risk for cesarean after dinoprostone use = 2.47 (95% CI = 1.14, 5.37).

TABLE 3.—*Cesarean Data by Study Group*

Patient Characteristics and Outcome	Study Group: Dinoprostone, n=16	Study Group: Control, n=6	P
Infant weight, grams ± SD	3,016 ± 244	3,325 ± 339	.47
Infant Apgar scores at 5 min ± SD	8.3 ± 0.3	8.5 ± 0.5	.78
Nullipara, No. (%)	12 (75)	4 (66)	.70
Previous cesarean section, No./total (%)	3/41 (7)	1/38 (2.6)	.62
Successful vaginal birth after cesarean, No. (%)	2/3 (66)	0/1 (0)	1.00
Preterm (<37 wk), No.(%)	3/6 (50)	1/4 (25)	.57
Indication for cesarean delivery, No. (%)			
Failure to progress ≥5 cm	5 (31)	4 (67)	.13
Failure to progress ≤5 cm	5 (31)	0 --	.12
Fetal distress	3 (19)	2 (33)	.47
Worsening medical condition	-- (3)	0 --	.15
Oxytocin infusion, hr ± SD	17.9 ± 2.6	18.1 ± 4.7	.98

dinoprostone group, but in the opposite direction from what was expected—that is, there was a significantly higher incidence of abdominal delivery in the dinoprostone group. There was no significant difference between the two groups in the number of patients who achieved spontaneous vaginal delivery.

Likewise, we were unable to show any significant shortening of the induction-to-delivery interval or a reduced use of oxytocin in the treated group as compared with the patients who received placebo. Because all patients had the gel instilled intracervically in the same manner, and the gel was stored at 4°C before use to prevent inactivation, these technical factors are not likely causes for the lack of a difference between treated and placebo groups.

As expected, there were significantly fewer failed inductions in the prostaglandin group compared with the placebo group, despite all having highly unpromising Bishop scores. (Patients were excluded from further analysis if good labor was not established or if delivery did not occur in the first 24 hours.) No instances of fetal distress or hyperstimulation could be ascribed to dinoprostone use. Once patients had achieved true labor, however, "failure to progress" was still the most common indication for abdominal delivery. This occurred about equally in those with an unduly protracted latent phase of labor (failure of the cervix to dilate 5 cm despite 24 hours of oxytocin administration) and in those who had 5-cm dilation but whose labor then arrested in the active phase. This latter group may have had inherent disproportion, although their fetuses were not significantly heavier (3,016 ± 244 grams versus 3,325 ± 339 grams). There were more nulliparas in the PGE_2 group who did not have vaginal delivery, which while not reaching statistical significance, may have clinical relevance. Patients who had had a previous cesarean section and those being induced prematurely (<37 weeks) did seem to have a higher rate of vaginal delivery than controls if they received dinoprostone, but because of the small number, no definite conclusion can be made. Table 3 summarizes the data from the cesarean section patients.

Discussion

The use of dinoprostone (prostaglandin E_2) gel for cervical ripening and inducing labor has been extensive over the past decade, although a commercially available preparation has only recently won approval from the Food and Drug Administration. Despite the plethora of studies of prostanoids for use for this indication, unequivocal evidence of their efficacy in lowering the cesarean section rate has not been clearly elicited. Nevertheless, some investigators have called for an end to the further investigational use of these agents.

On surveying the accumulated experience in the literature, we were unable to establish the efficacy of the intracervical application of dinoprostone for ripening of the cervix and the induction of labor despite favorable conclusions by some reviewers.[8,9] We limited our review to the use of intracervical prostaglandin E_2 gel. Table 4 summarizes these results.[10-18] Only the controlled studies were analyzed. One of the studies was not double blind, one used oxytocin as the control,[15] and two used only small control groups.[10,13] The use of vehicles of similar viscosities seemed fairly constant across studies, although three studies reported the use of a cross-linked starch polymer that may have less leakage from the endocervix.[4,15,17] This may be an important variable influencing the extent and rate of drug release. All but one of the articles included only patients with highly unripe cervices (Bishop score 4 or less).[13] Of the 12 studies analyzed, 9 used a dose of 0.5 mg, as we did. Some, however, used serial applications of the gel.[11,15] This certainly would have required a higher total dosage and a longer induction-to-delivery interval to achieve the same results, but may not be an unreasonable approach if urgent delivery is not an issue. The largest multicenter controlled study from Europe had a cesarean section rate of 16% in the prostaglandin-treated group (n = 416) and a rate of 21% in the control group (n = 404), a difference that was not statistically significant.[4] A comparable multicenter study in the United States, carried out by the Maternal-Fetal Medicine Network under the sponsorship of the National Institutes of Health, examined a carefully selected cohort of women past their due date.[3]

TABLE 4.—*Comparison of Preinduction Intracervical Prostaglandin E_2 (PGE_2) Studies in the Literature*

Source, Year	Subjects, No.	PGE_2-Treated/ Controls, No.	PGE_2 Dose, mg	Vehicle	Cesarean Section Rate: PGE_2 Group, No. (%)	Cesarean Section Rate: Control Group, No. (%)	P
Steiner et al, 1979[10]	44	38/6	0.1-0.3	Methylcellulose	7 (18)	--	--
Ulmsten et al, 1982[11]	50	25/25	0.5	Cross-linked starch polymer	0	0	--
Fuchs et al, 1984[12]*	15	10/5	0.4	Methylcellulose	1(10)	2(40)	NS
Nimrod et al, 1984[13]	45	30/15	0.25-0.5	Ethylcellulose	4 (13)	0 (--)	--
Sorenson et al, 1985[14]*	103	53/50	0.75	Methylcellulose	5 (12)	4 (15)	NS
Trofatter et al, 1985[15]*	59	39/20	0.5	Triacetin	9 (30)	8 (27)	NS
Yonekura et al, 1985[16]	48	25/23	0.5	Triacetin	10 (40)	5 (22)	--
Laube et al, 1986[17]*	45	30/15	0.25-0.5	5% Xylose	8 (26)	1 (7)	<.05†
Noah et al, 1987[4]*	820	416/404	0.5	Triacetin	67 (16)	84 (21)	NS
Ferguson et al, 1988[18]*	94	47/47	0.5	Cross-linked starch polymer	6 (13)	15 (32)	.05
Medearis, in press[3]*	262	171/91	0.5	Not stated	38 (22)	16 (18)	NS
This study	79	41/38	0.5	Methylcellulose	16 (39)	6 (16)	<.05†

*Breslow-Day test for homogeneity of odds ratios among the 8 studies indicates no significant difference ($P = .073$). Mantel-Haenszel statistics: estimated common odds ratio for cesarean section in PGE_2-treated group compared with controls = 0.86 (95% confidence interval = 0.66, 1.12).

†*P* values in bold type demonstrate significantly higher rate in PGE_2-treated group.

A total of 171 women had their labor induced after prostaglandin gel was instilled and had a cesarean section rate of 22% compared with an 18% rate in the 91 patients who received placebo; this, likewise, was not a statistically significant difference. We went on to do meta-analysis of the eight studies wherein cesarean section was looked at as an outcome variable.[3,4,12,14-18] A combined total of 791 subjects in the PGE_2 group was compared with 664 controls. Meta-analysis confirmed our impression that there is insufficient evidence that preinduction intracervical dinoprostone at this dosage favorably affects the cesarean section rate.

In summary, the results of this study concur with those of other larger studies, suggesting that the intracervical application of the dinoprostone gel may not be as effective an agent as has been thought by others. Whereas this single-dose trial did not show any reduction in the cesarean section rate, more favorable results may be obtained with sequential dosing, a larger intracervical dose, or a larger intravaginal dose. Investigation of these options and of alternative induction agents should continue.

The problem of the high rate of abdominal delivery after induced labor may lie not with the ripening agent, but rather with an adequate dose of oxytocin. An acceptable rate of cesarean delivery can be achieved when a policy of "active management of labor" using high-dose oxytocin is undertaken.[19] If the cesarean section rate is indeed the "bottom line," the efficacy of prostaglandins as a cervical ripening agent may not be of clinical relevance if the rate of abdominal delivery is not reduced.

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Conferences and Reviews

Coccidioidomycosis

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Coccidioidomycosis is a systemic fungal infection endemic to the southwestern United States and other parts of the western hemisphere. Although producing a wide range of disorders in healthy persons, immunosuppression predisposes to especially severe disease. Thus, a knowledge of the pathogenesis of coccidioidal infections and its relation to the normal immune responses is useful to understand the diversity of problems that *Coccidioides immitis* may cause. Diagnosis usually requires laboratory studies such as fungal culture or specific serologic testing. Fortunately, many patients do not need to be treated for the infection to resolve. Therapy for the more severe forms of coccidioidal infection was once limited to amphotericin B but now includes azole antifungal agents. These expanded alternatives now require physicians to weigh many factors in determining the best management for specific patients.

(Galgiani JN: Coccidioidomycosis. West J Med 1993; 159:153-171)

About 100 years ago, an Argentinean soldier was reported by a medical intern and his teacher to have lesions resembling mycosis fungoides that contained an organism resembling protozoa.[1] Shortly thereafter, two more cases were recognized by Emmet Rixford, a Stanford surgeon.[2,3] Although Rixford correctly proposed that these unusual infections might have originated in the San Joaquin Valley of California, their true fungal cause was not discovered until later,[4] and the public health dimensions of the infection, currently about 100,000 cases per year, were not appreciated until the 1930s.[5]

Once a distinctly regional disease of the Southwest, coccidioidomycosis is no longer a disease to be comfortably ignored by physicians elsewhere.[6-12] The advancing epidemic of the acquired immunodeficiency syndrome (AIDS) and immunosuppressing medical therapies such as cancer chemotherapy and organ transplantation have made the reactivation of dormant coccidioidal infections increasingly likely in patients throughout the United States. Because such infections are often life-threatening, there is little tolerance for delays in diagnosis if treatment is to be helpful, and therefore more rapid methods for diagnosis, now under development, will be important additions to laboratory testing. In addition, new antifungal agents have become available, and these have increased the options for treatment. Many physicians, especially those who treat only occasional coccidioidal infections, have not had the opportunity to learn the best use for these new agents. Finally, interest in the natural history and pathogenesis of *Coccidioides immitis* is broadening as well, and there is a growing understanding of both diagnostic and T cell-stimulating fungal antigens.

In this review I aim to identify in detail some of these recent developments and integrate them into an overall understanding of the disease. It is hoped this will serve both as a resource for those who need an update on coccidioidomycosis since previous reviews[13-16] and as a stimulus for new work into areas where substantial questions remain.

Epidemiology

The endemic regions for C *immitis* lie exclusively in the western hemisphere and nearly all between the 40-degree latitudes north and south (Table 1). Within the United States, the low deserts of Arizona and the Central Valley of California are the most intensely endemic. Recently an Indian skeleton dated at more than 1,000 years old has been found to have lesions containing spherules and represents the first conclusive evidence of mycotic infection in prehistoric North America.[17] Outside of the United States, endemic regions have been identified in Mexico and areas of both Central and South America. With few exceptions, the regions of endemicity are characterized as the "Lower Sonoran Life Zone."[18] The climate is arid, with a yearly rainfall ranging from 5 to 20 inches, and it has hot summers, winters with few freezes, and alkaline soil.

Within regions endemic for *C immitis*, infection can occur without any specific predisposition. Past estimates of the annual endemic risk of infection have been derived from the prevalence of reactivity among children. In Kern County, California, for example, reactivity in 1939 was 55% in elementary school students and increased to 68% in high school students. By 1964, reactivity in elementary

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ABBREVIATIONS USED IN TEXT

AIDS = acquired immunodeficiency syndrome
CF = complement-fixing [antigen]
CSF = cerebrospinal fluid
HIV = human immunodeficiency virus
IDCF = immunodiffusion complement-fixing
IDTP = immunodiffusion tube precipitin
Ig = immunoglobulin
TP = tube precipitin-reacting [antigen]

school was only 8% and increased to only 24% by high school.[19] This downward trend in rates has been corroborated by recent studies in the Tucson, Arizona, metropolitan area that have suggested that the annual risk is in the range of 2% to 4%.[20-22] Above this ambient risk, occupational dust exposure[23-26] and windstorms[27] have occasionally caused outbreaks.

TABLE 1.—*Geographic Regions Recognized as Endemic for* Coccidioides immitis

Geographic Region or Continent	*Specific Area*
United States	
Arizona	Southern deserts including the cities of Phoenix and Tucson
California	Parts within or near the Central Valley of the counties of Tehama, Butte, Glenn, Yolo, San Joaquin, Alameda, Stanislaus, Merced, Madera, Fresno, San Benito, Tulare, Kings, Monterey, Kern, San Luis Obispo, Los Angeles, Ventura, Riverside, Imperial, and San Bernardino; also the southernmost portion of San Diego County
Nevada	Southernmost tip
New Mexico	Portions of the southern third
Texas	Western portion, including the city of El Paso, and along the western Mexican border
Mexico	Adjacent to the western US border, western portions of the states of Sonora, Nayarit, Jalisco, and Michoacán, and central regions including Coahuila, Durango, and San Luis Potosi
Central America	The republics of Guatemala, Honduras, Nicaragua
South America	Argentina, Paraguay, Venezuela, Colombia, Brazil

In a review of the epidemiologic features of coccidioidomycosis, Pappagianis discusses the seasonal nature of new infections, which appear influenced by many factors including rainfall, sunlight, temperature, and the salt concentration of the soil.[28] How such factors can dramatically change the number of infections has been demonstrated by the record-breaking epidemic occurring in 1991 and 1992.[29] In Kern County alone, the reported number of cases exceeded 1,700 for the three months ending in November 1992,[30] and similar increases have been reported throughout the entire San Joaquin Valley. Neither of the two preceding winters' precipitation had been particularly heavy, a factor that has been associated with higher rates during the following summer.[26] An analysis of the timing of the rainfall has suggested a possible correlation between a greater-than-seasonal precipitation in the months of February and March and increased disease activity (Gavin Welch, Kern County Health Department, written communication, February 1993) (Table 2). Other climatic influences including the drought conditions of the past several years may also have contributed to the epidemic.

TABLE 2.—*Relationship of Annual Number of Reported Cases of Coccidioidomycosis in Kern County, California, for Years in Which February and March Precipitation Exceeded 4.00 inches**

Year	*Rainfall for February and March, inches*	*Reported Cases of* Coccidioides immitis *Infection, No.*
Normal (1982-1990)	1.9	253
1938	4.61	Not available
1978†	6.68	451
1991	4.33	1,181
1992	4.00	3,292

*Source of data: Gavin Welch, Kern County Health Department.
†Includes infections also attributed to winter dust storm (from Pappagianis and Einstein[27]).

Host-Parasite Biologic Processes

Mycology

Coccidioides immitis grows as mycelia in its saprobic form, producing arthroconidia that readily infect the lungs. Within the terminal bronchioles of the lung,[31] an arthroconidium sheds its hyphal outer wall layer and enlarges spherically, forming internal septations that contain endospores.[32-35] When mature spherules rupture, they release endospores in clumps embedded in a glycocalyx, and endospores continue in the spherule phase. If inoculated into saline solution or standard culture media, spherules revert to mycelial growth.[36] Using specialized techniques, spherules can be propagated in vitro,[37-39] and this has been useful for studies of spherule-associated antigens. The usual taxonomic classification based on a sexual phase has not been possible as both the mycelial and spherule phases of growth are asexual. An alternative approach using ribosomal subunit gene DNA homology has been employed to relate *C immitis* to other fungi.[40] In these studies, more than 1,700 bases of the 18S ribosomal gene were sequenced from strains of *C immitis*, five other human fungal pathogens, and four higher fungi. Of 1,565 sequence positions that could be aligned in all 10 taxa, 335 showed at least one substitution, and for *C immitis*, the fewest substitutions occurred in comparisons with *Blastomyces dermatitidis*, *Histoplasma capsulatum*, and *Trichophyton rubrum*. A tree of genetic relatedness illustrating the predicted evolutionary relationships is given in Figure 1. By this line of analysis, all of these pathogens would be classified as Ascomycetes.[41]

Pathogenesis and Innate Defenses

From studies in mice, only a few arthroconidia administered intranasally are necessary to produce an infection,[42] and it is surmised that most ambient infections of humans occur from only a single spore. Occasionally ex-

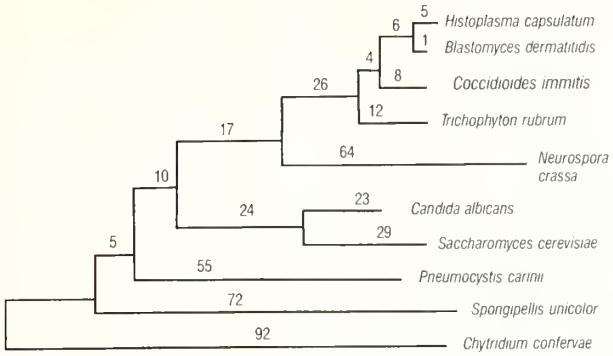

Figure 1.—This "tree" shows the genetic distances among species, based on pairwise substitutions among *Coccidioides immitis* and 9 other fungi. The number on each branch represents the number of DNA substitutions inferred to have been fixed on that branch (redrawn from Bowman et al[40]).

posure can be much more intense, such as during military maneuvers[26,43] or at archeologic excavation sites.[25,44,45] In these circumstances, the likelihood of symptoms and more widespread infection developing seems to be greater. After infection, the incubation period before initial symptoms ranges from one to three weeks.

Pathogenicity appears largely related to spherule resistance to eradication by even normal host defenses and to the inflammatory response that they engender. Fungal extracts can activate complement and attract human neutrophils in vitro.[46,47] These observations are consistent with the histologic finding of accumulated neutrophils, eosinophils, and other evidence of acute inflammation that is often present in portions of coccidioidal lesions.[48] Although measurable inhibition by neutrophils of arthroconidia and immature spherules has been reported, these effects are lost as spherules mature, and neutrophils show virtually no killing of any stage of coccidioidal growth.[36,49,50] The outer hyphal wall layer of arthroconidia may in part be responsible for the resistance to phagocytosis because physically shearing it from arthroconidia makes them more vulnerable to neutrophil ingestion.[51] Moreover, a protease capable of digesting antibodies and perhaps other opsonins has been isolated from spherules, and this might also increase the resistance to fungal attack.[52,53] Finally, the wall itself may provide a substrate to react with a variety of microbicidal intermediates that neutrophils release during the oxidative burst, thus blunting their otherwise lethal effects.[54] In combination, these observations suggest that the acute inflammatory response may slow fungal proliferation, but ultimately it is inadequate to arrest the disease process. Moreover, as new spherules are propagated within the infected tissue, they continue to be a source of acute inflammation, resulting in progressive suppuration and tissue destruction. Spherules of *C immitis* possess no known toxins,[55] nor is tissue infarction by vascular invasion a characteristic of coccidioidomycosis.[56]

Even though neutrophils are incompletely effective in controlling coccidioidal infection, other cellular defenses may play a greater role before antigenic stimulation of immunity. Using human peripheral blood natural killer cells or mononuclear leukocyte fractions enriched for monocytes, killing of endospores and arthroconidia, respectively, has been demonstrated even with leukocytes from patients without previous coccidioidal infection.[57-59] An interesting speculation arising from these observations is the possibility that these cellular defenses might eradicate early infections, conceivably without T-cell help. If this were the case, enhancement of T cell-independent defenses by response modifiers would be a potentially effective means of treating coccidioidal infections in patients with AIDS or others whose T lymphocytes are impaired.

T Cell-Mediated Immunity

A wide variety of studies have established T-lymphocyte immunity to *C immitis* as critical to the normal control of infections. An adoptive transfer of splenic lymphocytes from vaccinated mice protects recipient mice from lethal coccidioidal infections.[60] Cytokines including interferon gamma from such splenic lymphocytes promote macrophage killing of endospores in vitro,[61] and recombinant interferon gamma produces the same effect with murine peritoneal macrophages or human blood monocytes.[62,63] In humans, dermal delayed-type hypersensitivity, peripheral blood lymphocyte transformation, and the elaboration of interferon gamma to coccidioidal antigens are all evidence of T-cell immunity that normally develops after naturally acquired infection but is lacking where infection is progressive.[64-71] As is discussed later, patients with T-cell deficiencies are particularly vulnerable to widespread infections. Unrestricted infections may also occur in some patients who seem to have a selective susceptibility to coccidioidomycosis and do not exhibit generalized anergy.[72]

Despite all of these observations that implicate a T-cell requirement for controlling infection, details about how the T-cell response is regulated are largely unknown. Early studies of the protective effect of killed-spherule vaccines indicated that vaccination does not prevent infection but rather limits its spread.[73] More recently, comparisons of two inbred strains of mice, one sensitive and the other resistant to experimental coccidioidomycosis, indicate that both strains have delayed-type hypersensitivity early after infection. In mice of the sensitive strain, this reactivity is lost in association with increasing fungal antigenemia.[74,75] In other studies, serum containing analogous antigen activity was found to stimulate suppressor cells.[76] Whether similar events occur in humans is not known, although antigenemia and circulating immune complexes have been detected in patients during early and more chronic illness.[77-80] Serum antibodies also develop after infection, are of considerable diagnostic importance (discussed later), and to some extent, differences in the class of antibody response (especially immunoglobulin [Ig] E[81]) have been associated with differences in clinical illness. Even though there is no evidence that antibodies are protective, anti-idiotypic antibodies might be involved in T-cell regulation in coccidioidomycosis, as has been suggested in other diseases.[82]

Coccidioidal antigens used in past studies of T-cell re-

sponses have been complex heterogeneous preparations, and therefore a precise definition of the important antigens is only beginning to be learned. Kirkland and coworkers described a cell-wall antigen mixture from *C immitis* that stimulates a murine T-cell line derived from a mouse immunized with an attenuated strain of *C immitis*.[83] The T-cell line was also stimulated by mycelia-derived coccidioidin but not with exoantigens of spherules or irrelevant antigens. Also, a fusion protein was isolated from a mycelia-derived complementary DNA library that stimulated the T-cell line, and it is anticipated that a primary amino acid sequence will be learned from the continuation of that work. Another antigen has been isolated from the walls of spherules.[84,85] Apparently a glycoprotein in situ, the deglycosylated protein measures 33 kDa and reacts selectively with both antibodies and T lymphocytes from patients who have been infected with *C immitis*. Of additional interest, the expression of this protein is greatest in mature spherules and least in mycelia, a relationship that corresponds closely to differences in the potency of vaccines prepared from spherules or mycelia.[86,87] Work is now underway to learn the full-length sequence and to map regions that are important to both humoral and cellular responses.

Clinical Consequences of Infection

After infection is established, the range of subsequent manifestations is great (Figure 2). It is estimated that about two thirds of patients have no illness or at least have symptoms mild enough that medical attention is not sought. The only evidence of such infections is likely to be a positive coccidioidal skin test. The most common form of infection within the endemic regions is a subacute and usually self-limited pulmonary syndrome. In a few patients, however, the pneumonic process leads to various pulmonary sequelae, and in others, infection produces lesions outside the chest. Although these complications occur in only a small proportion of all infected patients, they are the most common manifestations seen by physicians outside of the endemic areas and may require extensive medical attention. Thus, keys to the appropriate management of patients with coccidioidomycosis are to recognize occurrences that are expected during a normal uncomplicated primary infection and, conversely, to identify as early as possible the cases of unusual or more extensive infection.

Pulmonary Infection

Initial manifestations. The clinical features of primary coccidioidal infection have recently been analyzed in 172 (97 male and 75 female) ambulatory University of Arizona students who were diagnosed during the four years before 1983 and their course compared with descriptions of previous cases.[88] The most frequent symptoms included fatigue (77%) and pulmonary symptoms of cough (64%), chest pain (53%), dyspnea (17%), and hemoptysis (4%). Fever was present in 46% of patients, arthralgia or myalgia was reported in 22%, and 22% had headache. There was a trend for symptoms to be more numerous in

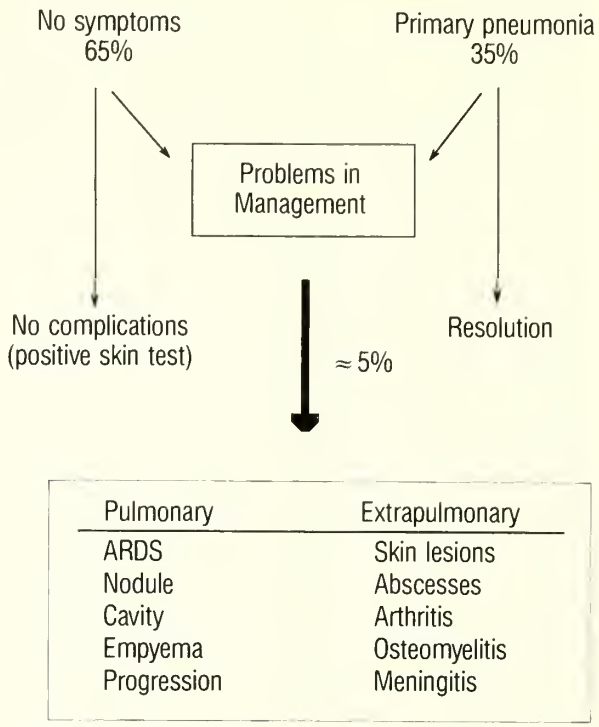

Figure 2.—The diagram outlines the clinical spectrum of coccidioidomycosis. ARDS = adult respiratory distress syndrome

men than in women. The most common skin reactions were a diffuse maculopapular evanescent rash (16% in men, 7% in women) and erythema nodosum (3% in men and 23% in women). Erythema multiforme is also well recognized to occur in association with early infection and may be more common in children.[13] Chest radiographs showed associated abnormalities of pneumonia (41%), cavities (8%), or nodules (4%). Pleural effusions were not noted in these patients, but are part of the spectrum of primary infection.[89] Effusions are ipsilateral, and cultures of pleural biopsy specimens usually grow *C immitis*. In addition, hilar adenopathy, usually unilateral and previously commonly noted on chest radiographs,[90-92] was not addressed in this review. The peripheral blood leukocyte count usually was below 10×10^9 per liter (10,000 cells per μl), but eosinophilia (greater than 5% of the total) was noted in 27% of patients. Erythrocyte sedimentation rates were often elevated.

The typical pattern for initial illness is not easily distinguished from various other respiratory tract problems by symptoms or from a routine medical visit. Yozwiak and associates prospectively analyzed students with respiratory complaints for symptoms and routine laboratory abnormalities that were significantly associated with coccidioidal infection.[93] By multivariant analysis, the following six factors appeared to behave independently and were used to construct a probability index for this infection: erythrocyte sedimentation rate above 28 mm per hour, male sex, erythema nodosum, endemic residence of less than four years, duration of symptoms less than one week, and an absolute lymphocyte count of less than 1.6

$\times 10^6$ per liter (1,600 cells per μl) (Figure 3).[93] A small proportion of patients with coccidioidomycosis had all six factors present, and in those cases the scale was specific. For most patients, fewer factors were present, and the risk of infected and noninfected patients overlapped substantially. Thus, in general, diagnosis requires a specific laboratory evaluation, as is discussed in a later section.

Usual clinical course. Of 172 otherwise healthy college students, 161 recovered without therapy, and only 9 had pulmonary complications: slowly resolving pneumonia in 6, persistent cavity in 2, and ruptured cavity in 1.[88] This is also the result for most cases complicated by pleural effusion.[89] Despite this eventual resolution, there was considerable cost and attendant morbidity.[20] Even without specific antifungal therapy for most patients, the cost of medical services for these patients was estimated

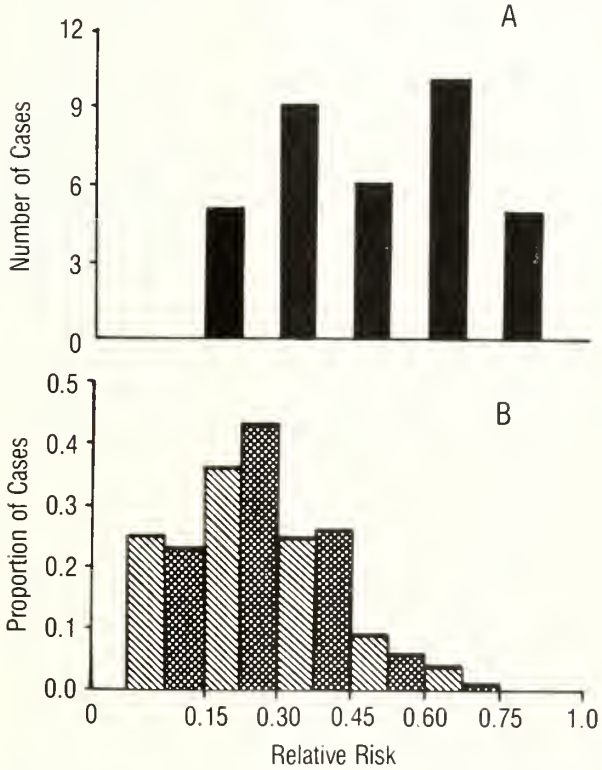

Figure 3.—The graphs show the distributions of the estimated likelihood of coccidioidal infection among 556 patients seeking medical attention for symptoms suggestive of coccidioidomycosis. The relative risk values are based on a standardized scale from 0 to 1 in which 1 represents the highest risk of disease. Graph A represents the relative risk distribution of 36 patients diagnosed with coccidioidomycosis. Graph B represents the relative risk distribution for those in whom the evaluation for coccidioidal infection was negative (hatched bars, n = 269 patients) and for those in whom infection was indeterminate (cross-hatched bars, n = 287 patients) (reprinted from Yozwiak et al,[93] with permission).

to be more than $70,000 (1983 dollars), and a similar cost was incurred in other patients without coccidioidomycosis in whom the diagnosis was entertained. The number of clinic visits required averaged more than six per student, about twice as many as for patients with mononucleosis, and management often extended for several months. Thus, even though the infection typically resolves, management commonly requires considerable attention over a protracted period of time.

Nodules. Coccidioidal pneumonia in about 5% to 7% of patients will evolve to form sharply circumscribed radiodense lesions, usually solitary and less than 6 cm in diameter. In most patients, these lesions are associated with no symptoms, and if a progression from the original coccidioidal pneumonia to the residual nodule is documented, then further evaluation is rarely necessary.

The major difficulty posed by these lesions is their resemblance to carcinoma. In a review of 200 solitary pulmonary nodules surgically resected from patients within the coccidioidal endemic region, 33.5% were found to be malignant.[94] Unfortunately, there are no accurate noninvasive means to exclude cancer. In 86% of persons with benign pulmonary nodules, serum anticoccidioidal antibodies are undetectable. Coccidioidal skin tests are often reactive, but this does not assure that the pulmonary lesion is not a second process. Because many of the lesions are peripheral, bronchoscopic biopsy frequently produces nondiagnostic tissue, and until recently most patients required a thoracotomy to remove the lesion. In reviewing the results from percutaneous fine-needle aspiration in 348 patients from medical centers within Phoenix, Arizona, Forseth and colleagues reported that 101 (29%) lesions yielded either spherules on smear or *C immitis* on culture,[95] thus saving the patient a more invasive procedure. Others have reported similar results.[96]

Cavities. Another possible sequela of the initial coccidioidal pneumonia is the development of a pulmonary cavity.[97,98] This occurs in about 5% of patients, and typical cavities are solitary, thin-walled, and peripheral (Figure 4). Cavitation is unusual in children[99,100] and less frequent in young adults than in older adults. The cavities are commonly asymptomatic, and about 50% will disappear within two years of their occurrence. Some cavities do cause problems, especially if radiographs show a surrounding infiltrate or an air-fluid level. Occasionally coccidioidal mycetoma can develop.[101-105] Common symptoms include cough, constant but relatively scant sputum production, chest pain in the region of the cavity, and hemoptysis. Fever, night sweats, or weight loss may also be present but are less frequent. Although infection occasionally spreads to contiguous segments of the lung, the process usually remains restricted to the original site of involvement. Diabetes mellitus is regarded as a risk for heightened morbidity associated with cavities,[106] but the documentation for this is not conclusive.

Considering the peripheral location of many coccidioidal cavities, rupture into the pleural space is a surprisingly infrequent event and most often develops in otherwise healthy young adults. In a series of 23 patients with this complication,[107] male patients outnumbered female patients 17 to 6, the median age was 24 years, 19 patients were white, and only 2 had diabetes mellitus. Of interest, only 8 patients had known of their infection before rupture. The symptoms are similar to those of a spontaneous pneumothorax, which is often the initial impression, leading to a possible delay in diagnosis. A useful differentiat-

ing point is the presence of an air-fluid level evident on chest radiograph in the pleural space that is typical of a ruptured cavity and unusual for a spontaneous pneumothorax. Once a ruptured cavity is identified, the mainstay of treatment is surgical repair.[107]

Diffuse coccidioidal pneumonia. Diffuse involvement of the lungs most commonly is the result of reticulonodular infiltrates (Figure 5) caused by hematogenous spread of the fungus[108] and is a manifestation of widespread infection. This is almost always a complication that occurs in immunocompromised patients, such as those with lymphoma, organ transplants, or AIDS.[22,109-111] Diffuse pneumonia can also be the result of primary infection developing in many parts of the lung simultaneously. Because ambient exposure within the endemic regions is unlikely to result in a high inoculum exposure, a history of unusually intense exposure rather than immunosuppression is more typical. In some instances, the radiographic differentiation of multicentric primary infections from diffuse reticulonodular infiltrates may be difficult.

Figure 4.—The chest radiograph is from an otherwise healthy patient with pulmonary coccidioidomycosis. Note the thin-walled cavity in the upper lobe of the right lung.

A few patients have infections that progressively involve greater and greater portions of the lung.[112] Symptoms often persist for years and include weight loss and fever in addition to those directly referable to the chest. Radiographs are characterized by both inflammatory infiltrates and fibrosis, often including bilateral apical cavitation, and these features distinguish this process from the more acute forms of diffuse pulmonary involvement.

Manifestations of Extrapulmonary Lesions

Infections due to *C immitis* outside the chest are almost always the result of hematogenous spread from an initial pulmonary focus. The fungus may spread asymptomatically outside the lungs more frequently than is clinically appreciated. For example, Rodenbiker and coworkers performed full ophthalmologic examinations on 53 patients with previous self-limited coccidioidal pneumonia and found asymptomatic chorioretinal scars typical of coccidioidal lesions in 4 (7.5%).[113] Similarly, some patients with transient recovery of *C immitis* from urine cultures had no identified extrapulmonary lesions and were managed without antifungal therapy.[114] Thus, for a clinically relevant definition, disseminated infections should include the identification of one or more destructive extrapulmonary lesions. Supraclavicular adenopathy is thought to represent thoracic extension by the lymphatic system,[115,116] but should be considered disseminated lesions and treated similarly to those resulting from hematogenous dissemination.

Figure 5.—The chest radiograph shows coccidioidal infection in a patient also infected with the human immunodeficiency virus. Note the reticulonodular infiltrates throughout both lungs.

Extrapulmonary lesions most commonly involve skin, joints, bones, and meninges. The frequency of lesions occurring in these various anatomic locations has been estimated in the past,[56,117] but many of the cases were identified because they were fatal, and it is possible that the record of disseminated infection is distorted as a result. A set of several hundred clinical case records was collected by an Armed Forces-Veterans Administration collaboration in the 1950s, before the availability of effective antifungal therapy, but a description of this group of patients has only recently been undertaken.[118] It is hoped that continued analysis of these records will provide a more quantitative picture of the various manifestations of disseminated infection.

Nonmeningeal sites of dissemination. The skin is the most common site of extrathoracic spread. Although cutaneous infections may occur anywhere, they often develop on the face (Figure 6). Papules and verrucous le-

sions are typical, but superficial plaques or subcutaneous abscesses also occur.[119] Symptoms associated with these lesions are often minor and evidence of acute inflammation on examination only slight. The histopathologic features of these varied lesions range from necrosis to granulomatous reactions and satellite lesions.[120] Skin biopsy of these lesions usually yields *C immitis* in culture, although finding spherules microscopically may be more difficult.

Bones and joints are also frequent sites of dissemination. Knee infection is common, often being a pure synovitis without evidence of bone involvement. In other cases, joint infections are more likely to have contiguous osteolytic lesions seen on x-ray films, most frequently involving vertebrae, wrists, hands, ankles, feet, pelvis, and long bones, in that order.[121,122]

Figure 6.—A skin lesion is shown on a patient with disseminated coccidioidomycosis.

In addition to skin and skeletal infections, lesions can occur anywhere throughout the body. For example, recent reports have focused on infections of the sella turcica,[123] the eye,[124] the larynx,[125-127] the external ear,[128,129] the thyroid,[130] the peritoneum,[131,132] prosthetic grafts of the femoral artery,[133] the placenta during pregnancy,[134] the female genital tract,[135,136] intestinal tract,[137] the liver,[138,139] urinary bladder,[140] and other urologic sites.[141-143]

Meningitis. A recent review of the natural history of coccidioidal meningitis has focused on the clinical course of 25 patients with meningitis that was diagnosed before the availability of antifungal therapy.[118] In that analysis, the most common symptoms of central nervous system involvement were headache (76%), vomiting (32%), nuchal rigidity (26%), confusion (8%), and diplopia (8%). The chance that meningitis occurred as the sole site of dissemination or as one of numerous sites was about equal. Patients with multisite dissemination had a median survival of 2 months whereas those whose dissemination involved solely the meninges had a median survival of 11 months. This confirms earlier reports that coccidioidal meningitis is nearly always lethal in two years.[144-148] In addition, other reports have identified a few patients in whom signs of cerebral or spinal vasculitis develop.[149,150]

Initial cerebrospinal fluid (CSF) findings included leukocyte counts ranging from 98 to 1,250 $\times 10^6$ cells per liter (98 to 1,250 cells per μl), and about two thirds of the cells were mononuclear. In a recent review it was noted that 70% of patients also have CSF eosinophilia (>10 $\times 10^6$ cells per liter or >0.10 eosinophils).[151] An unexpected finding from this study was that CSF pleocytosis tended to fall over time. Although an explanation for this pattern is not certain, the decrease could result from fibrosis encapsulating the foci of inflammation. Other CSF findings included protein concentrations ranging from 0.61 to 2.52 grams per liter (61 to 252 mg per dl) and glucose concentrations ranging from 0.5 to 4.1 mmol per liter (9 to 74 mg per dl).

Hydrocephalus is a common complication of coccidioidal meningitis, and in children it is usually present at the time of diagnosis.[152] Although the presence of dilated lateral ventricles and other findings by computed tomographic scanning have been adequate for detecting this problem, magnetic resonance imaging has been necessary to evaluate the aqueduct of Sylvius for patency.[153] Often hydrocephalus is a communicating type, as shown in Figure 7. In such cases a lumboperitoneal shunt is feasible and may offer some advantages over a ventriculoperitoneal shunt, which was most commonly installed in the past.

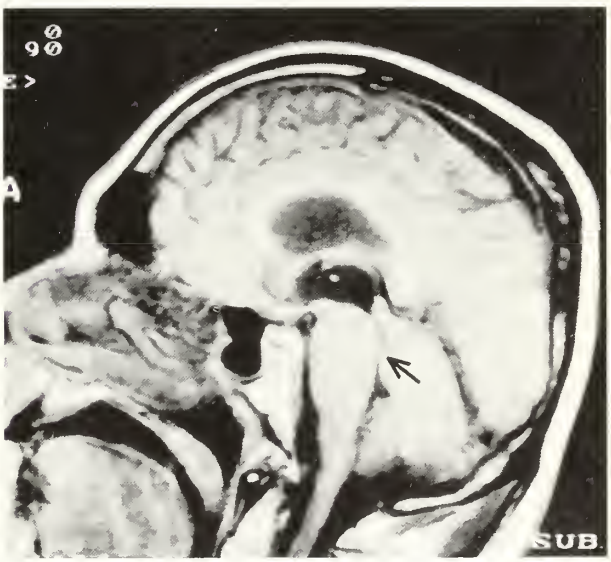

Figure 7.—A magnetic resonance image of a patient with coccidioidal meningitis complicated by hydrocephalus shows the third ventricle to be enlarged, but the aqueduct of Sylvius is patent, as indicated by the arrow.

Primary extrapulmonary inoculation. Rarely, cutaneous lesions can develop as the result of direct inoculation and do not represent extension from a pulmonary focus.[154-158] Primary cutaneous lesions develop painful suppurative sores, often with regional adenopathy, and usually heal without antifungal therapy.

Predispositions to Extrapulmonary Spread of Infection

Human immunodeficiency viral infection. Before 1987, only five patients with coccidioidal infection as a

complication of AIDS had been reported.[159-163] A report by Bronnimann and associates, however, described seven cases in Pima County, Arizona, and estimated that the annual risk of infection might be as high as 28% per year.[109] A subsequent prospective study has been carried out in the Phoenix and Tucson areas during a four-year period to determine more accurately the incidence of active coccidioidal infections occurring in patients infected with the human immunodeficiency virus (HIV).[164] Results from that study indicated with 95% confidence a risk of active infection to range from 8% to 41% during the period of study. This makes coccidioidomycosis one of the most frequent life-threatening complications for HIV-infected patients within the regions endemic for *C immitis*.

Why these rates are higher than for estimated skin-test-conversion rates for immunocompetent patients[21] or rates of infections for other immunosuppressed patient groups[22] is not clear. One possibility is that endemic exposure is higher than skin-test-conversion rates reflect. If this is the case, natural host defenses that normally prevent infection before T cell-dependent immunity is produced may be impaired in HIV-infected patients. An alternative explanation is that a reactivation of previously quiescent infections is contributing to the rates. Supporting this contention were the findings that overt infection was significantly associated with heightened immunodeficiency—$CD4^+$ count <250 cells $\times 10^6$ per liter, an established diagnosis of AIDS, and anergy to noncoccidioidal skin test antigens. Other factors, such as a history of previous coccidioidomycosis, prolonged residence within the endemic area, or the presence of a positive coccidioidal skin test, did not show a similar correlation as might be expected if reactivated latent disease was important. Clearly this issue needs resolving for physicians to counsel their patients.[165]

The clinical profile for coccidioidomycosis in HIV-infected patients was developed by a retrospective review of 77 previously unreported cases.[111] The most common presentation, occurring in 31 (40%) of the patients, was the radiographic finding of diffuse bilateral reticulonodular infiltrates (Figure 5). This was a serious illness for which the median survival was only one month, and the density of spherules within the lung tissue was great.[166] On the other hand, 20 patients (26%) had unilateral focal pulmonary infiltrates as their presenting complaint. Infections in these patients manifest a clinical course that would be difficult to distinguish from that of patients without HIV infection, and in this group during the period of follow-up after diagnosis, only 2 patients had died. Another 20 patients had various forms of extrathoracic dissemination including meningitis (9 patients), inguinal and other adenopathy (5 patients), skin lesions (4 patients), and hepatic lesions (2 patients). The course of these patients' infections varied widely, with many surviving for prolonged periods of time. In the remaining 6 patients, focal lesions were not evident and diagnosis was by serologic tests only. This last group also had more favorable survival times. Other complications have included peritonitis[131] and brain abscess.[167]

Many HIV-infected patients have had great difficulty handling coccidioidal infections, and for them treatment is critical. A few patients have been able to resolve their illness without treatment, and so it is possible that selected patients might be best served without an early initiation of therapy. As summarized in Table 3, treatment is nearly always indicated in patients with extrathoracic lesions, in patients with bilateral reticulonodular pulmonary lesions that are usually associated with fungemia, and in patients whose $CD4^+$ counts are low. On the other hand, because a positive skin test does not predict increased risk of reactivation, it is not in itself an indication for treatment. Moreover, a few patients who otherwise appear to be immunologically intact and to be handling their infection might well benefit from not beginning therapy. This last approach could save both cost and possible toxicity but is likely to produce anxiety in both patient and physician and would require close observation and frequent reevaluation.

TABLE 3.—*Guidelines for the Treatment of Patients Infected With the Human Immunodeficiency Virus Who Have Coccidioidomycosis*

Treatment indicated if
Extrathoracic dissemination
Diffuse pulmonary infection
Any infection in the presence of a $CD4^+$ count < 250 $\times 10^6$/liter
Observation indicated if
Asymptomatic positive skin test
Localized pulmonary infection, $CD4^+$ count is normal, and illness is resolving

Organ and bone marrow-transplant recipients. A renal transplantation program was established in southern Arizona in 1970, and its experience with coccidioidomycosis developing in patients with kidney transplants was reviewed in 1980.[22] The annual risk of infection was approximately 6% in the first year after engraftment and decreased to about half of this for subsequent years, roughly comparable to estimates of skin-test-conversion rates for the general population in the same area. The difference in the first year has been thought to be related either to reactivation (analogous to the possibility with HIV-infected patients) or to higher levels of immunosuppressive medications. Despite the relatively low incidence, infections progressed to dissemination in 12 of 18 patients and to death in 10. A similar rate of infection occurred in heart-transplant recipients, but dissemination and death occurred less frequently than in patients receiving kidneys.[168,169]

Because specific instances of the reactivation of previous coccidioidal infection after organ transplantation have occurred at centers outside the regions endemic for the fungus,[170-172] the safety of proceeding with organ transplantation in patients with a history of infection is in question. Recently we reviewed the records of 656 organ recipients from our renal and cardiac transplantation programs and identified 9 cases of coccidioidal infections

that had occurred before the patients received their grafts.[173] Five of these patients received one or another form of antifungal therapy after transplantation; in this group, no recurrent infections developed. In contrast, four patients received no antifungal therapy, and in two of them, recurrent coccidioidomycosis developed, and they died as a result. In addition, both of these patients were on heightened immunosuppressive therapy for acute rejection, another factor that might have contributed to recurrence. Also identified in our review were 11 other patients with positive coccidioidal skin tests before they received heart transplants. None of these had postoperative antifungal therapy, and none have had the infection recur.

This experience represents a beginning at understanding this problem and can be used to formulate tentative guidelines for evaluating and managing transplant candidates (Table 4). First, as with HIV-infected patients, a reactive coccidioidal skin test is a poor predictor of reactivation after immunosuppression. Second, as part of the transplantation evaluation, an extensive residence and travel history should be obtained to identify those who need screening coccidioidal skin tests. Three of our patients, including the two who ultimately died of recurrent infection, were identified only by serologic screening. Finally, our findings suggest that those with past coccidioidomycosis or positive pretransplantation serologic tests may need postoperative antifungal therapy to prevent reactivation. Whether these recommendations should be modified or expanded in the future will require experience with the management and outcome of more cases. To facilitate the exchange of this information, a data base has been established at the University of Arizona that can be reached using my address (see reprint request footnote at beginning of article). It is hoped that physicians who have experience with organ transplantation in individual patients with previous coccidioidal infections will contribute their observations to this resource so that increasingly rational guidelines can be developed.

Other forms of immunosuppression. A seminal report establishing *C immitis* as an opportunistic pathogen was that of Deresinski and Stevens, who reviewed the experience at Stanford University Medical Center (Palo Alto, California). They noted that infections were more likely to disseminate in patients with Hodgkin's disease than in those without immunosuppressing diseases or treatments.[110] In another report from the University of Arizona, 16 of 126 coccidioidal infections treated at that center were in patients with malignant neoplasms, uremia, collagen-vascular diseases, or those who had received recent immunosuppressive drug therapy.[174] In the immunosuppressed group, the rate of dissemination was 50%, and all had received immunosuppressive therapy. In both reports, the severity of the infection was wide ranging, with some patients surviving more than three years after the onset of their infection despite immunosuppression. Although coccidioidomycosis has not been frequent in those receiving bone marrow transplants, three centers (two outside of the endemic regions) have each had a patient with this complication.[175]

TABLE 4.—*Guidelines to Prevent Recurrent Coccidioidomycosis After Organ Transplantation*

Patient Finding	*Disposition*
History of endemic exposure	Test for coccidioidal antibodies and consider giving antifungal drugs during treatment of acute rejection
Positive skin test	Same as for history of endemic exposure
History of coccidioidal illness	Give antifungal drugs after engraftment or if antibodies are detected

Other acquired predispositions. Pregnancy has been regarded as a risk for women, especially during the third trimester and the peripartum period. In reviewing 74 published reports and 41 unpublished cases from Pappagianis, Peterson and colleagues indicated that of 38 women in whom coccidioidomycosis was diagnosed in the third trimester, 26 (68%) had disseminated disease and 18 (47%) died.[176] With amphotericin B treatment of first- and second-trimester infections, mortality was 19% compared with 66% in untreated patients. In contrast, of 23 patients diagnosed during their first trimester, only 5 had disseminated disease and 3 died. Usually the infants were uninfected, although neonatal coccidioidomycosis has been reported.[177,178] These alarming statistics included early reports from central California in which the general health of some of the women was poorer than is likely the case today. Moreover, even with relatively low estimates of annual infection rates and the number of pregnancies per year within the endemic regions, the predicted number of serious infections from coccidioidomycosis is far greater than obstetricians practicing in these areas have found. This point was documented by Wack and co-workers by surveying the number of coccidioidal infections reported among 47,120 pregnancies.[179] Although 178 infections would be expected during the third trimester, assuming the annual risk is 3% and 50% of the women had not had a previous infection, these authors were able to find only 10. Four infections were presumptive diagnoses only, none resulted in death, the delivered infants were healthy (two women had elective abortions not related to infection), and only two infections progressed to dissemination. Nonetheless, both cases of disseminated infection occurred in women whose infection began late in their third trimester, other case reports continue to describe a similar pattern,[180-182] and recent in vitro studies have shown a blunted lymphocyte response to coccidioidal antigens near term and postpartum.[183] Taken together, these observations suggest that within the endemic area coccidioidal infections actually occur fairly infrequently during contemporary pregnancies. Moreover, when symptoms of coccidioidomycosis do occur late in or soon after pregnancy, they are often associated with serious complications.

Genetic factors. Whether certain racial groups are at higher risk of having disseminated lesions has been a topic of extensive debate. Disseminated infections have

developed in Filipinos, African Americans, Mexican Americans, and Native Americans out of proportion to their representation in the general population, and as a result it has been suggested that this might be due to genetic differences. From early data, Filipino patients accounted for 22% of the reported cases of dissemination whereas they constituted only 0.25% of the general population.[184] This proportion was 175 times higher than for whites. Critical analysis of the methods used in those reports has raised questions about whether the intensity of exposure, nutrition, or the presence of other diseases might be more important factors than race.[185] Observations during a severe California dust storm in 1977, in which exposure was unlikely to be biased, have reasserted that differences in a predisposition to dissemination between races do in fact exist. In one report, patients identified through contact with a reference serologic laboratory were categorized either as having disseminated infection or as being symptomatic without dissemination.[186] It was reported that infection in 53.8% of African-American patients and 38.4% of Asians (including Chinese, Japanese, Korean, and Vietnamese but excluding Filipinos) was classified as disseminated, in contrast to that in only 11.2% of white patients. A similar pattern with a smaller number of cases was reported from a naval base after the same dust storm.[187] Thus, at present it appears likely that African- and Asian-American patients are at greater risk than are whites.

Other evidence of genetic links to disseminated infection is derived from an association with specific blood groups. Deresinski and associates reported that disseminated infection was disproportionately common in patients with blood group B.[188] Similarly, Cohen and colleagues showed dissemination to be associated with both the B and AB blood groups in kidney transplant recipients or those undergoing hemodialysis.[22] The significance of this association has not been developed, although it is presumed to relate to the linkage of blood group antigens with immunoregulatory genes. If this is the case, then it would be expected that dissemination would also be associated with one or another HLA type. Although early studies have failed to demonstrate this,[189] contemporary typing methods have not been applied to the question.

Diagnostic Approaches

Culture of the Organism and Its Identification

The definitive method of establishing the diagnosis of coccidioidomycosis is by isolating the fungus from a clinical specimen. *Coccidioides immitis* is not fastidious and readily grows on most media used in clinical microbiology laboratories. It is also a fairly rapidly growing fungus, often detectable within five days and sometimes as early as two days after the medium has been inoculated.

Colonial structure of the mycelial phase is not diagnostic, and further studies are necessary to establish the identity of the organism. In the past, this was done by inoculating mice or using special in vitro procedures to produce endosporulating spherules[190,191] or by extracting mycelial growth with thimerosal (Merthiolate) to test for a species-specific antigen.[192,193] Another approach has been to grow specimens on a commercial medium that indicates the presence of *C immitis* by a color change. Unfortunately, this strategy has not yet become sufficiently specific for clinical use.[194] More recently, a species-specific DNA probe has become available in a commercial kit so that species can be identified on the day that growth is detected.[195]

Despite the value of recovering *C immitis* in culture, this poses a possible risk to laboratory personnel because the mycelial phase is highly infectious.[24,29] For this reason, if a mycelial organism is observed in a culture, the petri dish or container should not be opened except in a biologic containment cabinet and by experienced personnel. Similarly, if infection due to *C immitis* is suspected, clinicians should note that possibility on the laboratory request slip.

More rapid than culturing *C immitis* and equally specific are identifying spherules in infected tissue or cytologic preparations.[196-200] Although occasionally other structures may resemble spherules,[201,202] this seldom poses a problem. In difficult cases, viewing the hematoxylin-eosin–stained structures under fluorescent light can sometimes be helpful because *C immitis* will autofluoresce.[203] The direct examination of specimens is faster than growing *C immitis* in culture but is not as sensitive.[204] Therefore, both procedures should routinely be requested from the laboratory.

Antibody Detection

For the past half century, detecting anticoccidioidal antibodies has been an important means of establishing a diagnosis of coccidioidomycosis.[205,206] A thorough discussion of conventional testing procedures was published recently[207] and is beyond the scope of this review. It may be useful, however, to summarize the types of testing currently available, some new information emerging about the nature of the fungal antigens used to detect antibodies, and new approaches that are under development for future use.

The two major antigens used to detect anticoccidioidal antibodies are the tube precipitin-reacting (TP) antigen—so called because of the precipitin button that formed in the bottom of the test tube in the originally described "tube precipitin" test—and the complement-fixing (CF) antigen. During primary infections, IgM antibodies against the TP antigen are usually found in serum earlier than CF antibodies and disappear sooner, although exceptions to this rule can occur. In contrast, TP antibodies are not usually found in more chronic infections whereas CF antibodies are typical. The concentrations of TP antibodies have never been related to the prognosis. On the other hand, the concentration of CF antibodies is generally in proportion to the extent of disease, and by standardized laboratory procedures, detecting antibodies in dilutions greater than 16-fold is significantly associated with extrapulmonary infections. The ability of CF antibodies to activate complement and to persist for long periods is typical of IgG immunoglobulins.

TABLE 5.—*Commercially Available Diagnostic Tests for Coccidioidomycosis*

Commercial Kit Test	Correlation With Reference Tests: Tube Precipitin (TP)	Correlation With Reference Tests: Complement Fixation (CF)	Comment	Source
Immunodiffusion TP (IDTP)	Yes	No	Has largely supplanted the original TP, even in reference laboratories	Kaufman et al, 1985[208]; Huppert and Bailey, 1963[210]; Huppert and Bailey, 1965[212]
Immunodiffusion CF (IDCF)	No	Yes	Usually used as a screen with quantitation provided by CF test	Johnson et al, 1984[209]; Huppert and Bailey, 1965[211]; Wieden et al, 1983[214]
Latex	Yes	No	Screening test only; should always be confirmed	Huppert et al, 1968[219]
ELISA	Yes	Yes	New test; full validation awaits further documentation	Gade et al, 1992[221]

ELISA = enzyme-linked immunosorbent assay

Although the traditional methods for detecting anti-TP or anti-CF antibodies are well established, neither is available as a commercial kit, and both are difficult to adapt to general-purpose clinical serologic laboratories for occasional use. In their stead, dual immunodiffusion procedures that can be more readily supplied commercially have been developed as surrogate procedures to detect antibodies of the same specificity as the original TP and CF tests.[208-217] Although the immunodiffusion tests are considered to be highly specific and at least as sensitive as the original methods, this evolution has introduced some confusion in terms because there are two immunodiffusion tests, one mimicking the TP test (IDTP) and the other mimicking the CF test (IDCF), depending on the reagents used (Table 5).[208-212,214,219,221] Like the TP test, the IDTP results are reported qualitatively as either positive or negative. Usually the IDCF is also reported qualitatively, and, if positive, would be followed by the standard CF test to obtain quantitative results.

Other tests are available for detecting coccidioidal infections but are at this time of more limited value. Latex agglutination tests have been used with some degree of success and have been recommended by some as a rapid method for screening serum for more specific studies.[218-220] More recently, an enzyme-linked immunosorbent assay has been introduced that has also been proposed for screening and may be more specific than latex tests.[221] Although useful, the results from these methods have not yet been extensively correlated with results from TP or CF tests.

As useful as detecting anticoccidioidal antibodies has been for diagnosing coccidioidomycosis, negative studies do not exclude the diagnosis. This is especially the case early in the course of primary infection[80] or in immunosuppressed patients. For example, a third of patients with AIDS in whom bilateral reticulonodular pulmonary infiltrates develop have had undetectable anticoccidioidal antibodies by conventional tests.[111,222] More sensitive procedures such as radioimmunoassay or enzyme-linked immunosorbent assay may improve antibody detection but require much more purified antigens to avoid nonspecific activity. Purifying relevant antigens has not been easy because extracts of *C immitis* are complex and their glycoprotein nature has posed technical difficulties for good separation. In recent years, both TP and CF antigens have begun to be characterized in some detail.[215,217,223-227] As a result, it is possible that synthetic or recombinant antigens should become available as reagents in the future.

Fungal Antigen Detection

Rather than rely on a patient's humoral response, an alternative serologic approach to diagnosis is to assay for circulating antigens of the fungus itself, as has proved useful in histoplasmosis.[228,229] Several studies have reported detecting coccidioidal antigens in the serum of patients with either acute or chronic infections (Table 6).[77-80] The move from these observations to a clinically available procedure has not yet occurred, however. As with antibody detection, the availability of more purified reagents will likely result in assays that are within the competence of clinical laboratories.

Defining the Extent of Infection

Once a diagnosis has been established, it is important to determine whether the infection has spread beyond the chest and, if so, how extensively. As was discussed ear-

TABLE 6.—*Detecting Circulating Coccidioidal Antigen as a Diagnostic Test*

Cases	Findings	Source
Mice		
Acute infection	Transient antigenemia*	Cox and Kennell, 1988[75]
Patients		
Acute infection	>50% with antigen in first 2 weeks*	Galgiani et al, 1982[80]
Chronic pulmonary infection	73% with immune complexes containing coccidioidal antigen	Yoshinoya et al, 1980[77]
Disseminated infection	56% with antigen†	Weiner, 1983[78]

*Results were obtained using an enzyme-linked immunosorbent assay.
†Results were obtained using a radioimmunoassay.

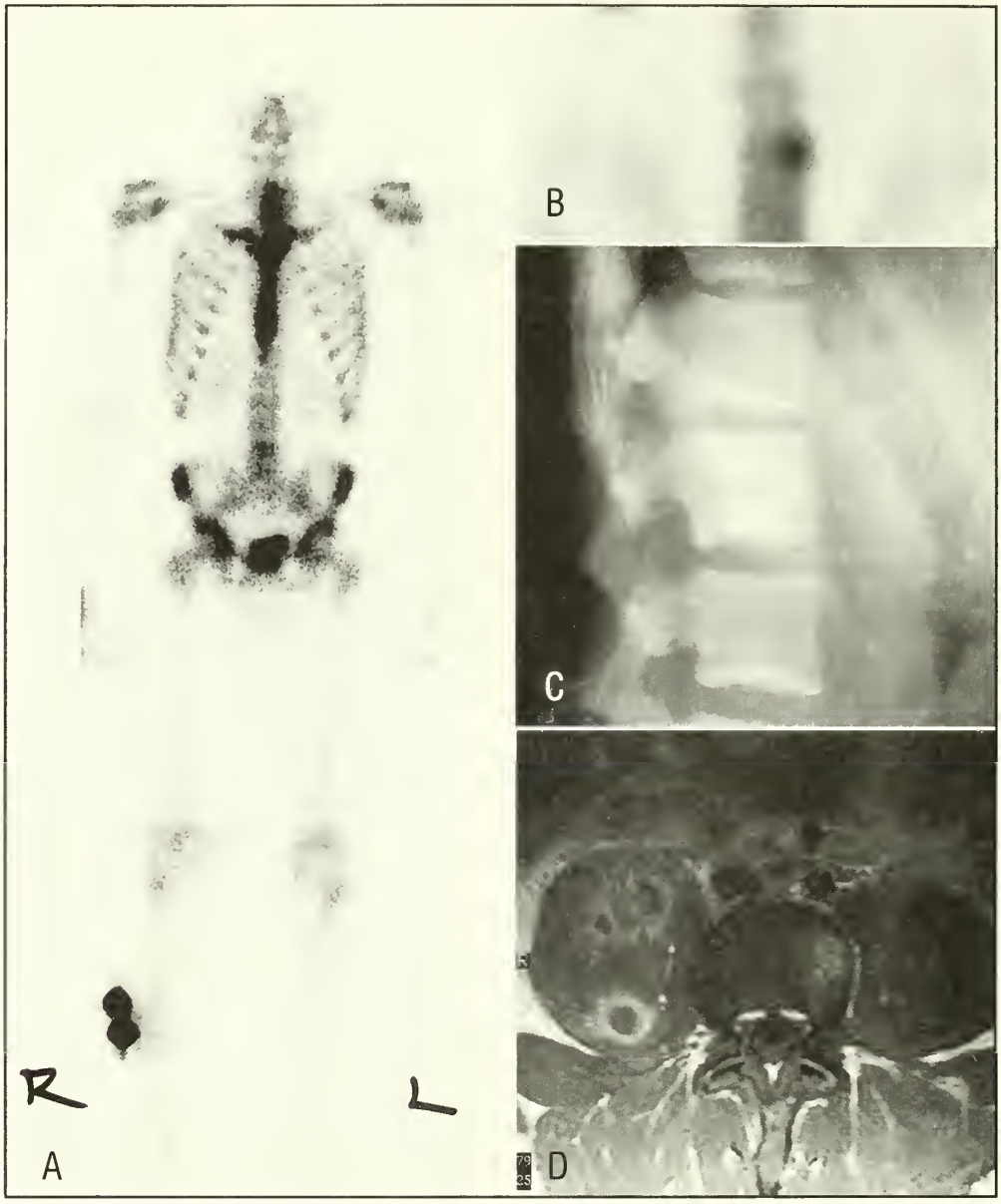

Figure 8.—Imaging techniques are shown that were used to define the extent of disseminated coccidioidomycosis in a patient. **A,** A bone scan was done because of a complaint of minor lower back pain; it showed subtly abnormal uptake in the second lumbar vertebra. **B,** Tomographic scanning of the second lumbar vertebra produced higher resolution and demonstrated asymmetry of the abnormal uptake. **C,** Planar radiographs confirmed a lytic lesion to be present in that region. **D,** Magnetic resonance imaging of the spine confirmed the findings in the second lumbar vertebra and also showed a lytic lesion in the fourth vertebra with associated abscesses in the surrounding muscles. These images were used to follow the progress of therapy and to determine the need for surgical debridement in addition to antifungal therapy. (A, B, and D are courtesy of Maria C. Tartak, MD, and Kelly McAleese, MD.)

lier, coccidioidal lesions often include an acute inflammatory component, and as a clinical correlate, they usually exhibit a focal nature. For this reason, a careful history and physical examination that detects no recent unexplained complaints of pain or evidence of inflammation is a sufficient evaluation for the possibility of extrathoracic spread for most patients with early respiratory tract infections. The presence of such symptoms should lead to more specific diagnostic imaging studies, which might include plain radiographs, computed tomographic scans, magnetic resonance studies, ultrasonograms, or nuclear isotope scans (Figure 8).[230,231] Headache is a frequent symptom of patients with early coccidioidal infections, and, fortunately, in most patients it does not indicate the presence of meningitis. But for patients with persistent headache or headache associated with nausea, vomiting, mental status changes, or other neurologic findings, a lumbar puncture is indicated to examine the CSF for the presence of pleocytosis, depressed glucose concentration, elevated protein concentration, or CF antibodies.

Therapeutic Strategies

Initial Pulmonary Infections

Clearly most primary coccidioidal infections resolve without therapy. Furthermore, despite the availability of new antifungal agents for the treatment of primary infections, there in fact exists no persuasive evidence that any treatment is useful for either shortening the course of the initial illness or preventing more serious problems from arising. Although it is likely that some patients with an initial infection would benefit from treatment, physicians within the endemic areas do not agree about who should be treated or for how long.

The patients for whom there is the most agreement are those whose T-cell immunity is deficient, as indicated earlier. The selection of therapy for such patients follows the guidelines I outline for extrapulmonary dissemination. A second group that is perhaps likely to benefit from therapy are those with infection produced by a large number of arthroconidia simultaneously because the likelihood of complications in this group appears to be higher than in persons with the usual endemic exposure.[44] The goal of such therapy is to inhibit fungal proliferation temporarily as host immune responses develop for continued control. Because rapidity of drug action may be important in this situation, many physicians think that amphotericin B is the preferred antifungal agent and that treatment should be continued for a cumulative dose of at least 1.0 gram (for a recent review of the use of amphotericin B, see Gallis and co-workers).[232] Once a patient has improved, therapy may be completed over an additional several months with an oral azole antifungal agent such as ketoconazole, fluconazole, or itraconazole.

Finally, there are other patients with symptoms and extent of pulmonary infection that are compelling, but the threshold for these indications is not the same for different physicians, and, again, there are no results from clinical trials to help with this decision. Patients in that category most likely should be given a trial of a month to a year of treatment with an oral azole agent.

Chronic Pulmonary and Extrapulmonary Dissemination (Excluding Meningitis)

In 1957, amphotericin B was first reported to be effective for the treatment of coccidioidomycosis in a patient with cutaneous lesions of the face.[233] Since then the documentation for amphotericin B efficacy in this disease has been surprisingly scant. Hardenbrook and Barriere reviewed the literature for amphotericin's efficacy in coccidioidomycosis, and these authors were able to identify 103 patients in 34 publications.[234] Only seven reports included more than four patients. Overall, 73 patients responded to treatment. These reports are complemented by more than three decades of unpublished experience that has resulted in a consensus that the most fulminant cases of coccidioidomycosis are best treated with amphotericin B. On the other hand, many patients do not have fulminant infections, but rather have chronic or subacute manifestations. This group of patients has been the focus of several clinical trials of azoles.[235-239] A review of newer antifungal agents and their pharmacology has been published recently.[240]

For the past decade a large collaborative effort, sponsored by the National Institute of Allergy and Infectious Diseases and now known as the Mycoses Study Group, has brought focus and systematic approaches to the study of coccidioidomycosis and to other invasive fungal infections. A workshop report published in 1980 laid the foundations by outlining study design requirements.[241] Over the past decade, a standardized approach has evolved for assessing response to therapy. The studies shown in Table 7 were not done for strict comparison.[237,239] Even so, comparison is useful to some extent because the studies were carried out by the same collaborative group and, except for the study of ketoconazole, they followed uniform methods of measuring response.

The 400-mg-per-day doses of itraconazole and fluconazole were similar to the 200-mg-per-day dose of Sch 39304. As shown in Table 7, relapses of responding patients were encountered after drugs were stopped, so the rates for durable responses were lower. It should be emphasized that the ketoconazole results were estimated using more stringent criteria of response, and, to a large extent, this difference may account for the discrepancy between its lower response rates as compared with those obtained with the newer agents. In fact, these results do not clearly indicate the superiority of any one of the newer drugs over ketoconazole. This may be a particularly important point to bear in mind because the newer agents are considerably more expensive and because none have yet obtained US Food and Drug Administration endorsement for the treatment of coccidioidomycosis.

Also shown in Table 7 are untoward events that were possibly attributable to the drugs used in the various studies. Using 400 mg per day, about 95% of patients could tolerate prolonged courses of ketoconazole, itraconazole, or fluconazole. When higher doses of ketoconazole were used, side effects clearly became more numerous. Not apparent from these figures are differences in minor but nonetheless discomforting gastrointestinal side effects, and, in general, most investigators think that the newer triazoles such as fluconazole and itraconazole are better tolerated than ketoconazole. In January 1993, the Mycoses Study Group began a randomized, double-blind study comparing the use of fluconazole with that of itraconazole, and it is hoped that results from this trial will better define the relative value of these two agents.

Meningitis

With the introduction of amphotericin B, survival with coccidioidal meningitis improved.[146,242-249] But to be effective, amphotericin B had to be administered repeatedly into the cerebrospinal space, and courses of treatment lasted many months or even years. Moreover, as reviewed by Labadie and Hamilton, overall reported survival was only 57%, varying substantially among different reports depending on the specific technique of drug

TABLE 7.—*Summary of Mycoses Study Group Trials With Azole Antifungal Drugs for the Treatment of Nonmeningeal Coccidioidomycosis*

Drug	Dose, mg/day	Patients, No.	Treatment Results: Response, %	Relapse, %	1 Year Remission, %	Stopped Due to Toxicity, %
Ketoconazole*	400	56	23†	9	21	6
	800	56	32†	44	18	17
Itraconazole‡	400	51	57	16	49	6
Fluconazole§	200	73	34	39	21	4§
	400	25	61	36	39	
Sch 39304‖	100 or 200	54	66	¶	¶	4

*From Galgiani et al.[239]
†Response was defined by a different method.
‡From Graybill et al.[237]
§Number represents the number of patients in whom drug toxicity for all doses combined limited their treatment.
‖Data represent work in progress and have not yet been published in final form.
¶Drug was withdrawn before completion of the study.

administration, drug dosing, patient factors, and length of observation.[246]

The possibility of substituting oral therapy with azoles was investigated soon after they were available, and some of the early experiences that followed are summarized in Table 8.[250-252] Ketoconazole has not proved widely applicable for this disease because at least 1,200 mg per day of the drug has been needed, and side effects at this dose often cannot be tolerated. In addition, in all of these reports, all but one patient received amphotericin B either concurrent with or before the azole. Thus, it was difficult to be sure how much of the response was attributable to the azole component of the therapy.

To resolve this situation, the Mycoses Study Group initiated a trial of fluconazole for the treatment of coccidioidal meningitis.[253] Only patients with untreated meningitis or active meningitis after previous therapy with amphotericin B failed were included, and during the study other antifungals were not administered. The dose of fluconazole was 400 mg per day, and treatment was evaluated by repeated measurements of CSF and other abnormalities using a predefined scoring system. By the fall of 1990, 50 patients were enrolled. By chance, exactly half of the enrolled patients had not received previous therapy, 41 were male, and 9 were HIV infected. The response for both groups combined was 79%, ranging from 70% for patients without previous therapy to 88% for patients who had relapsed after past treatment. In reviewing the baseline characteristics for the two groups, it appeared that by the time previously treated patients were enrolled in this study they had slightly milder disease, and it is possible that this difference may have accounted for that group's higher response rate. During the study, 10 responding patients have died of unrelated causes, including AIDS in 6 and stroke, pulmonary embolus, Hodgkin's disease, and urosepsis in the others. All of the other responders have now completed more than two years of therapy and are doing well. Of the 10 patients for whom therapy failed, 2 HIV-infected patients died, 2 patients were switched to amphotericin B, and 6 patients were continued on a regimen of fluconazole, but the dose was increased to 800 mg per day.

TABLE 8.—*Preliminary Reports of Azole Therapy for Coccidioidal Meningitis*

Azole Drug	Daily Oral Dose, mg	Relation to Amphotericin B Administration	Patients, No.: Treated	Improved
Ketoconazole*	≥ 1,200	Before	5	5
Fluconazole†	50-400	Concurrent	7	4
		Before	7	5
		None	1	1
Itraconazole‡	300-400	Concurrent	3	3
		Before	5	4

*From Craven et al.[250]
†From Tucker et al.[251]
‡From Tucker et al.[252]

Responses were generally achieved within eight months, and the rate of response was not affected by either HIV coinfection or the presence of hydrocephalus. In the first four months, improvement is most attributable to reduced symptoms, whereas the improvement of various CSF measurements occurred more gradually. From a practical standpoint, this meant that patients would start feeling better within a month or two, even though objective measures of improvement would take considerably longer to manifest.

It should also be appreciated that in some patients, not all evidence of disease activity has completely resolved even after many months of treatment. For example, of 20 responding patients who had lumbar punctures repeated 20 or more months after starting therapy, 5 still have leukocyte counts of 20 or more cells $\times 10^6$ per liter. Similarly, the glucose concentration was between 1.7 and 2.2 mmol per liter (31 and 39 mg per dl) in 3 patients, and the protein value was between 0.5 and 3.12 grams per liter (50 and 312 mg per dl) in 9 of 16 patients, none of whom had hydrocephalus. Overall, 15 patients had at least one of these CSF variables abnormal. Thus, despite the generally favorable pattern, there is also considerable heterogeneity in the rate and completeness of the resolution of evaluated abnormalities.

To summarize current treatment options for coccidioidal meningitis, fluconazole has emerged as an attrac-

tive alternative to intrathecal therapy. The response rate of 79% shown recently would seem at least as good as that for amphotericin B.[253] On the other hand, 21% of patients did not have a response at a dosage of 400 mg per day, so there is clearly room for additional improvement in the therapy for this disease. It is encouraging that some of the patients for whom therapy initially failed appeared to do better on higher doses of fluconazole, and perhaps additional dose-ranging studies will solve some of the residual problems. Alternatively, it may still be necessary to use amphotericin B in some patients. Finally, most investigators are reluctant to stop azole treatment, even after many years of therapy. In a recent compilation of 16 patients who have stopped therapy with any of several oral azoles, including ketoconazole, itraconazole, or fluconazole, 12 patients relapsed (David A. Stevens, MD, written communication, July 1993). Because adverse drug reactions with fluconazole have been few, it would seem advisable to continue therapy until more is known about the safety of discontinuing treatment.

Future Directions for Research

With the development of azoles for the treatment of coccidioidomycosis, considerably more options are available than were a decade ago. Even so, the disease remains a therapeutic challenge and one to test new antifungal drugs and new treatment strategies. Most recently, lipid or liposomal formulations of amphotericin B raise the hope of reduced toxicity, which in turn may permit the use of higher and more effective doses.[254] Another approach has been to identify entirely new classes of antifungal agents such as those that inhibit cell-wall synthesis.[255] The chitin synthase inhibitor, nikkomycin, is one such drug developed by Bayer, and this agent has proved to be an effective orally administered treatment of coccidioidomycosis in experimental murine infections.[256] Unfortunately, this promising drug has been withdrawn from clinical trials by the sponsor. One can only hope that this decision might be reconsidered or that another farsighted pharmaceutical manufacturer might step in to continue the drug's development. Another lead for new classes of antifungal drugs emanates from the observation that cyclosporine has in vitro and in vivo inhibitory effects on *C immitis*.[257] Although cyclosporine itself is too toxic to be used for its antimicrobial effects, other related compounds might be more selective.[258] Finally, a therapeutic role for interferon gamma has theoretical and experimental support.[62,63] Only time will tell whether this or another cytokine will find a place in the treatment of coccidioidomycosis.

In addition to the continued need for new therapies, our understanding of the biology of this pathogen remains incomplete. That most infected patients have the power to heal themselves should be strong stimulus to learn more about the details of the immune response. To do this will likely require the participation of scientists trained in modern immunologic, biochemical, and genetic approaches. Such studies will rightly be viewed as ambitious undertakings by scientists who have generally preferred to study less complex or more established experimental problems. On the other hand, the possibilities for unexpected findings are equally great, and it can only be hoped they will attract more fundamental work on this pathogen in the years ahead.

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Atherosclerosis—Reversal With Therapy

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Evidence for atherosclerosis reversal comes from studies in animals wherein atherosclerosis is induced and then allowed to regress, autopsy studies of starved humans, and angiographic studies testing antiatherosclerosis treatment. Animal models and autopsy studies have provided detailed histologic and biochemical descriptions of regression. Cellular and subcellular information exists on what can occur, but because the same lesions are not reexamined, what actually does occur is unknown.

Studies of isolated arterial cell systems and intact lesions indicate that atherogenesis involves at least the following: Increased permeability of the endothelium to macromolecules such as low-density lipoprotein; platelet adherence to areas of functional endothelial injury or denudation; the entrance of monocytes or macrophages and lymphocytes into the subintimal space; and the secretion of growth factors by platelets, injured endothelium, and macrophages. These processes can be initiated or enhanced by various vasoactive agents that induce endothelial cell constriction with the opening of endothelial junctions. These processes also can recruit smooth muscle cells from the media to the subintima where they proliferate. Proliferating smooth muscle cells, along with macrophages, can internalize lipids and lipoproteins to form foam cells. Subintimal smooth muscle cells can also synthesize collagen, elastin, glycosaminoglycans, and other connective tissue elements that trap lipoproteins. Peroxidative injury increases the atherogenic potential of both cholesteryl ester-rich (low-density) and triglyceride-rich (very-low-density and intermediate-density) lipoproteins. Steep oxygen gradients within the arterial wall create local conditions for free radical generation, and any increase in residence time of lipoprotein particles can be atherogenic. In summary, there are many areas where treatment may retard or reverse atherogenesis.

Angiographic trials that identify and track individual human lesions have shown that reducing known atherogenic risk factors can lessen coronary and femoral atherosclerosis. But they provide no information on events within arterial wall cells or the intracellular matrix. They deal only with lesions that intrude into the vessel lumen and obtain measurements at infrequent intervals. The weight of evidence is that regression is possible, but there is no consensus on the most effective therapy. The challenge for future trials is to select optimal targets for intervention among the known atherogenic processes.

(Blankenhorn DH, Hodis HN: Atherosclerosis—Reversal with therapy. West J Med 1993; 159:172-179)

In 1967 Ost and Stenson treated 31 patients with atherosclerosis with regimens of 3 to 6 grams of nicotinic acid a day. Three showed improvement on femoral angiograms after a treatment period of three years, accompanied by an increase in pulse volume and improved walking capacity. The lipid levels achieved by niacin therapy were not reported, but it is probable that they were reduced.[1]

Eight patients with familial hypercholesterolemia were treated by Thompson and co-workers with repeated plasma exchange, and three showed measurable improvement in coronary artery and supravalvular aortic lesions.[2]

Barndt and colleagues reported treating 25 patients with hyperlipidemia with diet, lipid-lowering medication (primarily clofibrate and neomycin), and antihypertensive medication (if indicated).[3] Nine showed regression in femoral atherosclerosis (primarily early lesions) after 13 months. Patients showing regression were those with a substantial reduction in blood total cholesterol levels from 8.05 to 6.35 mmol per liter (311 to 246 mg per dl), triglycerides from 4.08 to 1.63 mmol per liter (362 to 143 mg per dl), and systolic and diastolic blood pressure levels from 132 to 123 mm of mercury and 85 to 79 mm of mercury, respectively. Patients showing progression did not have notable reductions in these risk factors.

Kuo and associates reported that treatment with combined colestipol and niacin therapy could stabilize atherosclerotic coronary artery lesions for periods as long as

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ABBREVIATIONS USED IN TEXT

CLAS = Cholesterol Lowering Atherosclerosis Study
HDL = high-density lipoprotein
LDL = low-density lipoprotein
NHLBI = National Heart, Lung and Blood Institute

seven and a half years. This evidence was based on serial coronary angiographic examinations in 25 patients.[4]

3 Influential Early Trials

Femoral Artery Trial With Selective Lipid-Lowering Therapy

Duffield and co-workers conducted an unblinded but randomized trial in which 24 patients (average age, 56 years) with advanced femoral atherosclerosis were treated with lipid-lowering drugs assigned according to their Fredrickson phenotype.[5] Entry criteria were claudication of six months' duration and plasma cholesterol levels of more than 6.47 mmol per liter (250 mg per dl). Patients with diabetes mellitus, diastolic hypertension, and rest pain were excluded. There were 12 drug-treated subjects (8 with type II, 3 with type III, and 1 with type IV hyperlipidemia) and 12 "usual care" patients whose lipid levels were untreated (8 with type II, 1 with type III, and 3 with type IV). Patients with type II hyperlipidemia were treated with a regimen of 12 to 24 grams of cholestyramine resin a day plus 3 to 6 grams of niacin. Patients with type IV hyperlipidemia were treated with niacin; those with type III were given clofibrate. Diet in both groups included 30% of calories as fat with a polyunsaturated to saturated fat ratio of 1 and a cholesterol intake of less than 250 mg per day.

Angiograms were repeated after a mean period of 19 months. In the interval between angiograms, total blood cholesterol levels averaged 6.03 mmol per liter (233 mg per dl) in treated patients versus 7.43 mmol per liter (287 mg per dl) in patients receiving usual care, triglycerides 1.86 mmol per liter (163 mg per dl) in treated versus 2.96 mmol per liter (260 mg per dl) in patients receiving usual care, high-density lipoprotein (HDL) cholesterol 1.54 mmol per liter (59.6 mg per dl) in treated patients versus 1.09 mmol per liter (42.3 mg per dl) in those receiving usual care, and LDL cholesterol 3.88 mmol per liter (150 mg per dl) in treated patients versus 5.10 mmol per liter (197 mg per dl) in those receiving usual care. Among 144 femoral segments in treated patients, 10 showed progression; among 156 segments in the usual-care group, 27 showed progression, a difference significant at the .01 level. This study is noteworthy despite the small number of subjects (too few for a formal per-patient test of treatment effects). It demonstrated that lipid-lowering therapy selected according to the lipid transport pattern can retard advanced femoral atherosclerotic lesions.

Pioneering Coronary Artery Trial

The National Heart, Lung and Blood Institute (NHLBI) Type II Study was a randomized, placebo-controlled, double-blind coronary angiographic study.[6] It tested the use of 24 grams per day of cholestyramine in subjects with type II hyperlipoproteinemia and overt coronary artery disease, excluding those with 75% or more stenosis of the left main coronary artery. A criterion for entry was LDL-cholesterol levels above the 10th percentile of the general population after a month of a low-cholesterol low-fat diet. Average entry levels were as follows: total cholesterol, 8.36 mmol per liter (323 mg per dl); triglyceride, 1.87 mmol per liter (164 mg per dl); HDL cholesterol, 1.01 mmol per liter (39 mg per dl); and LDL cholesterol, 6.50 mmol per liter (251 mg per dl); the two trial groups were evenly matched. The average entry blood pressure was 122/79 mm of mercury, 43% of subjects smoked, 26% of subjects were sedentary, and again the two trial groups were matched. A low-fat diet reduced LDL-cholesterol levels 5% in both groups. During drug treatment, LDL-cholesterol levels in the placebo group were reduced an additional 5% and LDL-cholesterol levels in the cholestyramine group were reduced 26%. Triglyceride levels in both groups were increased 25%.

The original study design called for 250 patients randomly assigned to two treatment arms, but recruitment was stopped after 54 months when 143 patients had been randomly allocated. In all, 57 patients in the placebo group and 59 cholestyramine-treated subjects had second angiograms after five years. Angiograms were evaluated by human panelists with the temporal sequence and treatment masked. Results from three separate panels of three angiographers were combined for the final analysis. On average, the panelists evaluated 5.4 lesions per subject. After the blind was broken, subjects were classified as having definite progression, probable progression, definite regression, probable regression, mixed response, and no change.

Trial results were as follows: significant per-subject differences between drug and placebo use were not detected; cholestyramine use significantly retarded progression in lesions with 50% or greater stenosis ($P < .05$); and an increased ratio of HDL to LDL cholesterol predicted lesion stabilization. In 1989, 54 film pairs from the study were reevaluated by the quantitative procedure of Brown and associates.[7] This confirmed the occurrence of mixed lesion response and indicated that the initial severity of stenosis correlated strongly with new total occlusion and with disease progression. The influence of the NHLBI Type II trial on later studies has been substantial because it led later investigators to test the use of more aggressive lipid-lowering therapy (drug-induced changes in total and LDL-cholesterol levels were not large, and triglyceride levels increased); it demonstrated that both progression and regression of lesions could occur in the same subject; it indicated that lesion severity at baseline influenced treatment response, with more severe lesions showing greatest benefit; and it introduced the use of human panel reading for evaluating films.

First Coronary Angiographic Trial Testing Diet

The Leiden Intervention Trial, which was started in 1978 and completed in 1981, recruited 61 patients with

stable angina and one or more lesions exceeding 50% stenosis who were not candidates for coronary artery bypass grafting.[8] The trial was not randomized or blinded; however, coronary angiograms were evaluated by readers who did not know blood lipid levels or the order of examination. All patients were assigned to a vegetarian diet that reduced saturated fat and cholesterol intake while increasing the intake of polyunsaturated fat. It was estimated that the diet at entry provided 11% of calories from saturated fat and 8.5% from unsaturated fat and that daily cholesterol intake was 88 mg per 1,000 calories. After a year, diet estimates indicated that 6.6% of calories were from saturated fat, 16.8% from polyunsaturated fat, and daily cholesterol intake was 30 mg per 1,000 calories.

Of 53 who started the diet, 4 died in the first year (3 with myocardial infarction, and 1 suddenly) and 7 patients had coronary artery bypass grafting. Angiography was not repeated in three patients (because of a malignant tumor in 2 and refusal in 1). Studies were repeated in 39 patients, and films were evaluated both by visual inspection and computer analysis.[8] Of the 39 patients, 21 showed progression. Among the 18 without progression, total cholesterol reduction was 9%. Lesion progression was strongly related to the total cholesterol:HDL-cholesterol ratio, and no coronary lesion progression occurred in patients with a total cholesterol:HDL-cholesterol ratio of less than 6.9 throughout the study or in those who had reduced a high ratio at baseline to less than 6.9. The most important finding of the Leiden study was the suggestion that lesion progression can be arrested by dietary modification without weight loss. Before this report, the literature on atherosclerosis regression in humans was limited to autopsy studies in starved populations.[9]

There were other noteworthy aspects of the Leiden Intervention Trial: The first parallel use of human visual reading and fully automated computer lesion measurement showed agreement in the classification of subjects with a stable lesion versus those with progression; as in the NHLBI Type II Study, lesion status at baseline was shown to influence treatment effect, with the greatest benefit to lesions greater than 50% stenosis; and the first within-group analysis (in this case because there was no control group) was useful in ranking the magnitude of risk factor effects.

6 Recent Coronary Angiographic Trials

Cholesterol Lowering Atherosclerosis Study

In the first angiographic trial in which clear evidence of atherosclerosis regression was demonstrated, combined therapy with colestipol and niacin was tested.[10] A pretrial of drug therapy was used to identify subjects with responsive lipid levels. The Cholesterol Lowering Atherosclerosis Study (CLAS) randomly allocated 188 nonsmoking men with previous coronary artery bypass grafts; 162 subjects had two-year angiograms, and 103 had four-year angiograms. Colestipol-niacin treatment produced large decreases in total cholesterol levels from 6.37 to 4.65 mmol per liter (246 to 180 mg per dl), total triglycerides from 1.72 to 1.25 mmol per liter (151 to 110 mg per dl), and LDL cholesterol from 4.43 to 2.51 mmol per liter (171 to 97 mg per dl). Drug treatment increased HDL-cholesterol levels from 1.15 to 1.57 mmol per liter (44.6 to 60.8 mg per dl). Coronary angiograms from the study have been evaluated by both human panel readers[10] by modification of the method used in the NHLBI Type II Study and by fully automated quantitative coronary angiography.[11] The two methods measure somewhat different but overlapping lesion populations, with panel readers addressing more severe lesions,[12] but they agree on treatment effects. Drug treatment produced a significant reduction in the number of native artery lesions that progressed ($P < .03$) and the percentage of patients with new lesion formation ($P < .04$). Drug treatment also produced a significant reduction in the number of patients with new lesion formation ($P < .04$) and other adverse changes ($P < .03$) in the bypass grafts. At two years, regression was found in 16.2% of the drug-treated group compared with 3.6% of the placebo-treated group ($P < .01$). The evidence for benefit retained strong statistical significance after the cohort was divided at the midpoint for an entry cholesterol level of 6.24 mmol per liter (241 mg per dl).

In all, 103 subjects remained on their assigned treatment with blinding maintained for a total of four years and had a third angiogram.[13] Changes in the levels of blood lipids, lipoprotein cholesterol, and apolipoproteins were maintained, and at four years significantly more drug-treated subjects showed nonprogression (52% drug group versus 15% placebo group, $P << .01$) and regression (18% drug group versus 6% placebo group, $P = .04$) in native coronary artery lesions. Significantly fewer drug-treated subjects had new lesions develop in native coronary arteries (14% drug group versus 40% placebo group, $P < .001$) and bypass grafts (16% drug group versus 38% placebo group, $P < .001$). Again, the evidence for benefit retained strong statistical significance after the cohort was divided at the midpoint for an entry cholesterol level of 6.24 mmol per liter (241 mg per dl).

A within-group analysis of diet records in CLAS subjects in the placebo group showed that dietary changes that reduced blood cholesterol levels could reduce the incidence of the formation of new coronary artery lesions.[14] The baseline diet of the entire placebo group had a total fat content that averaged 32% of total calories and a daily cholesterol intake of 258 mg. A total of 64 men, in whom new lesions did not develop during the first two study years, made dietary changes that reduced total plasma cholesterol levels from 6.29 to 5.95 mmol per liter (243 to 230 mg per dl). They significantly reduced dietary total fat, saturated fat, monounsaturated fat, and cholesterol and increased polyunsaturated fat. The major steps to accomplish this were the substitution of low-fat meat and dairy products for high-fat meat and dairy products. Another 18 men in whom new lesions developed did not reduce their cholesterol level from a baseline level of 6.24 mmol per liter. They made no notable dietary changes except to increase their polyunsaturated fat intake.

Subjects in CLAS also had femoral angiograms.[15] The two-year treatment effect on femoral atherosclerosis in

this study was considerable but was less pronounced than the benefit observed in coronary arteries and aortocoronary bypass grafts. The annual change rate in computer-estimated atherosclerosis, a measure of lumen abnormality, was evaluated between treatment groups.[16] A significant per-segment treatment effect was found in segments with moderately severe atherosclerosis ($P < .04$) and in proximal segments ($P < .02$). When segmental measures of computer-estimated atherosclerosis were combined into a per-patient score using an adaptation of the coronary scoring procedure used in the NHLBI Type II Study, a significant treatment effect was observed ($P < .02$).[15]

A pilot study of carotid ultrasound imaging was included in CLAS.[17] In all, 78 subjects (39 drug- and 39 placebo-treated) had ultrasound studies at baseline and two and four years. Computer images were processed to measure common carotid far-wall thickness. Computer operators were blind to the treatment group. The carotid intima-media thickness measured by ultrasonogram was correlated at baseline with visually read angiographic stenosis and at two years with a robust computer measure of carotid atherosclerosis. Drug-treated subjects showed substantial progressive reduction in carotid thickness at two and four years. Placebo-treated subjects showed significantly increased wall thickness at two and four years with differences in the change in thickness between the two groups significant at both times ($P << .01$). Reduced levels of apolipoprotein B and increased levels of HDL cholesterol and HDL-associated apolipoprotein C-III were significant predictors of carotid wall thinning. These findings indicate that carotid atherosclerosis at a stage before lesions intrude into the vessel lumen can be reduced by colestipol-niacin treatment. They also indicate the feasibility of image-processed carotid ultrasonographic trials of two years' duration and include 50 subjects per treatment arm to test early atherosclerosis treatment.

Program on the Surgical Control of the Hyperlipidemias

The largest trial reported to date tested lipid lowering by the partial ileal bypass operation.[18] The principal end points were coronary angiographic and clinical findings, total mortality, and morbidity or mortality due to coronary heart disease. The study population consisted of 838 patients who had survived a first myocardial infarction 6 to 60 months before being randomly allocated for the control (n = 417) or surgery (n = 421) group. The average age was 51 years, and 90.7% were men. Eligible subjects were required to have a total plasma cholesterol level of at least 5.69 mmol per liter (220 mg per dl) or an LDL-cholesterol level of at least 3.62 mmol per liter (140 mg per dl) if their total plasma cholesterol level was between 5.18 and 5.67 mmol per liter (200 and 219 mg per dl) on a phase II diet for six weeks. Major exclusion criteria were hypertension of greater than 180/105 mm of mercury, body weight 40% above ideal, diabetes mellitus, previous cardiac operation, pacemaker implantation, and left main coronary artery stenosis of greater than 75%.

The mean follow-up period was 9.7 years. The primary end point of the trial was death due to any cause. Secondary end points were cause-specific death (determined through a blinded review by an external committee) and recurrent confirmed or suspected myocardial infarction. Additional secondary end points were nonfatal myocardial infarction with electrocardiographic and cardiac enzyme changes, coronary artery bypass grafting, percutaneous transluminal coronary angioplasty, cardiac transplantation, and peripheral vascular operation.

When compared with the control group at five years, the surgery group had a total plasma cholesterol level 23.3% lower (4.71 versus 6.13 mmol per liter [182 versus 237 mg per dl], $P << .01$); an LDL-cholesterol level 37.7% lower (2.66 versus 4.30 mmol per liter [103 versus 166 mg per dl], $P << .01$); and an HDL-cholesterol level 4.3% higher (1.06 versus 1.04 mmol per liter [41.0 versus 40.2 mg per dl], $P = .02$). The most common side effect of the partial ileal bypass procedure was diarrhea. Other more serious side effects were kidney stones, gallstones, and intestinal obstruction.

Overall morbidity and mortality due to coronary heart disease were not significantly reduced, but the rate of death due to coronary heart disease and confirmed nonfatal myocardial infarction combined was 35% lower in the surgery group (125 versus 82 events, $P < .001$). Overall mortality in the surgery subgroup with an ejection fraction of greater than or equal to 0.50 was 36% lower (control versus surgery, 0.39 versus 0.24, $P = .02$). During follow-up, 137 control-group and 52 surgery-group patients underwent coronary artery bypass grafting ($P << .01$).

A comparison of baseline coronary arteriograms with those obtained at three, five, seven, and ten years consistently showed less disease progression in the surgery group ($P < .001$). This study is important because there is a prolonged follow-up with a sustained reduction of blood lipid levels, and improvement in coronary angiographic anatomy has been shown to result in reduced cardiac mortality and morbidity. This study remains a landmark, although the role of partial ileal bypass as a procedure for the management of hypercholesterolemia has been greatly reduced by the effectiveness of current lipid-lowering drugs.

Familial Atherosclerosis Treatment Study

The Familial Atherosclerosis Treatment Study was a three-arm trial (colestipol-niacin, colestipol-lovastatin, and conventional treatment) conducted in subjects with hyperlipoproteinemia that also showed that improved coronary angiographic anatomy is associated with reduced cardiac morbidity.[19] A total of 146 men 62 years of age or younger, with elevated apolipoprotein B levels and a family history of coronary artery disease, were randomly assigned to one of three therapeutic strategies. All patients had evidence of coronary atherosclerosis on a baseline arteriogram, with at least one vessel showing 50% stenosis or three showing 30% stenosis.

In the niacin-colestipol-treated group (average age 47

years, 22% smokers, and 44% with a history of hypertension), the colestipol therapy was begun at a dose of 5 grams, three times a day with meals, and increased to 10 grams, three times a day after ten days. Metamucil and dietary bran were used to control constipation. Niacin therapy was started at 125 mg twice a day and gradually increased to 500 mg four times a day (with meals and at bedtime) at one month and 1 gram four times a day at two months. If the LDL-cholesterol level did not fall below 3.10 mmol per liter (120 mg per dl) after three months, the dose of niacin was increased to 1.5 grams (3 tablets) four times a day, but no further.

In the lovastatin-colestipol-treated group (average age 48 years, 23% smokers, and 34% with a history of hypertension), lovastatin therapy was begun at a dose of 20 mg twice a day (in the morning and at bedtime). If the LDL-cholesterol level did not fall below 3.10 mmol per liter after three months, the dose of lovastatin was increased to 40 mg twice a day.

In the conventional therapy group (average age 47 years, 26% smokers, and 28% with a history of hypertension), patients received placebos for colestipol and lovastatin. For purposes of blinding, the lovastatin placebo dose for a patient assigned to conventional therapy was doubled each time the lovastatin dose was doubled for a patient assigned to receive lovastatin and colestipol. If baseline LDL-cholesterol levels exceeded the 90th percentile for their age (43% of the group), patients on conventional therapy received colestipol instead of its placebo.

In matched coronary angiograms at baseline and 2.5 years later, the borders of each lesion and the catheter were manually traced from selected frames onto a standard form. For lesions classified previously by visual inspection as unchanged or definitely changed, two selected frames were traced for each view. For "possibly changed" lesions, three frames were traced for each view, each by two technicians. All tracings were reviewed for accuracy by an experienced technician and were then digitized and processed. The diameter of the lumen at the point of greatest local narrowing (minimum diameter) and nearby normal diameters were measured, in millimeters, with the catheter used as a scaling factor. The two principal measures of disease were the minimum diameter and the percentage of stenosis:

$$\% \text{ Stenosis} = 100\,(1 - DM/DN),$$

where DM denotes the minimum diameter and DN normal diameter. Each estimate was an average of the estimates for the tracings measured, which averaged 3.1 per film (range, 2 to 12).

In the conventional therapy group, 46% of the patients had definite lesion progression (and no regression) in at least one of nine proximal coronary artery segments; regression was the only change in 11%. By comparison, progression (as the only change) was less frequent among patients who received lovastatin-colestipol (21%) and those who received niacin-colestipol (25%), and regression was more frequent (lovastatin-colestipol group, 32%; niacin-colestipol group, 39%; $P < .005$). When lesions were stratified by baseline severity, those with 50% or greater stenosis showed average regression, those with less than 50% stenosis showed only a reduction in average progression. Multivariate analysis indicated that a reduction in the level of apolipoprotein B (or LDL cholesterol) and in systolic blood pressure and an increase in HDL-cholesterol levels correlated independently with the regression of coronary artery lesions.

Clinical events of death, myocardial infarction, or revascularization for worsening symptoms occurred in 10 of 52 patients assigned to conventional therapy as compared with 3 of 46 assigned to receive lovastatin and colestipol and 2 of 48 assigned to receive niacin and colestipol (relative risk of an event during lipid-lowering treatment, 0.27; 95% confidence interval, 0.10 to 0.77).

University of California, San Francisco, Specialized Center of Research Intervention Trial

Subjects in the University of California, San Francisco, Specialized Center of Research Intervention Trial were between 19 and 72 years old and had clinical features of heterozygous familial hypercholesterolemia, such as tendon xanthomas and LDL-cholesterol levels above 5.18 mmol per liter (200 mg per dl) with total triglyceride levels below 7.12 mmol per liter (275 mg per dl) while on restricted dietary saturated fat and cholesterol.[20] Patients without tendon xanthomas were included if they had an LDL-cholesterol level above 6.47 mmol per liter (250 mg per dl) or an LDL-cholesterol level of greater than 5.18 mmol per liter (200 mg per dl) and a first-degree relative with tendon xanthomas. Patients with previous angioplasty, coronary bypass grafting, or multiple infarcts were excluded, as were patients with systemic diseases other than atherosclerosis or hypertension.

Subjects were randomly assigned by sex and age to test and control groups. Both groups received dietary counseling. The test group received aggressive drug therapy to reduce LDL levels with combinations of lipid-lowering agents. These patients were initially given as much as 30 grams of colestipol and as much as 7.5 grams of niacin daily, as tolerated. Of the 40 patients in the treatment group, 36 took niacin, 25 of whom consistently took more than 1.5 grams daily. In addition, 28 patients took 30 grams and 4 took 15 grams of colestipol daily throughout the study. When lovastatin became available as an investigational drug, it was given also; 16 patients took 40 to 60 mg of lovastatin daily in dual- or triple-drug combinations. At the start, the control group was treated with diet alone. Later this group was offered 15 grams per day of bile acid-binding resin. Fourteen patients elected to take colestipol. Seven men took it for an average of 19 months and seven women for an average of 20 months. The control group included those treated with diet alone and those treated with diet plus resin.

Coronary angiography was repeated after two treatment years. The primary outcome variable was a change in the cross-sectional percentage area of stenosis, averaged for all lesions in each subject. All other quantifiable

lesions were analyzed. The mean change in percentage of area of stenosis among controls was +0.80%, indicating progression, whereas the mean change for the treatment group was −1.53%, indicating regression ($P = .04$ by 2-tailed t test for the difference between groups). The effect of the baseline lesion status on the treatment response was not analyzed. Regression among women, analyzed separately, was also significant. When analyzed separately, women in this study showed more lesion benefit to therapy than did men. The change in the percentage of area of stenosis was correlated with LDL-cholesterol levels on the trial.

This trial is important because it demonstrates that regression can occur in women with a substantially greater change in lesions than that observed in men, and it extends information on regression to asymptomatic persons with hyperlipoproteinemia (92% were asymptomatic).

Life-style Heart Trial

The Life-style Heart Trial tested a comprehensive risk reduction program that included a low-fat vegetarian diet, smoking cessation, stress management, moderate aerobic exercise, and group support.[21] The treatment group diet allowed no animal products except egg white and one cup per day of nonfat milk or yogurt containing approximately 10% of calories as fat and 5 mg per day or less of cholesterol. Twice-a-week group discussions led by a clinical psychologist provided social support including stress management training. Subjects were asked to exercise for three hours per week and to maintain target heart rates for 30 minutes of each exercise session.

In all, 22 subjects in the life-style-change group were compared with 19 subjects randomly assigned to a usual-care control group who were not asked to make life-style changes. Patients having angiograms for clinical reasons unrelated to the study were screened, and among 96 eligible patients, 53 were randomly assigned to the experimental group and 43 to the control group. Major entry criteria were patients aged 35 to 75 years of either sex and having measurable coronary atherosclerosis in a nondilated or nonbypassed coronary artery. Left ventricular ejection fractions of greater than 0.25 were required. Randomization was accepted by 28 in the treatment group and 20 in the control group. Control group patients had higher entry total, LDL- and HDL-cholesterol, and triglyceride levels: 6.34, 4.32, 1.35, and 2.45 mmol per liter, respectively (245, 167, 52, and 217 mg per dl), than treatment group subjects, but differences at baseline between the randomized groups were not statistically significant.

Treatment group subjects made substantial life-style changes. The average exercise time was increased from 11 minutes per day to 38. Dietary fat and cholesterol that averaged 31% of calories and 213 mg per day, respectively, on entry were reduced to 7% of calories and 13 mg per day, respectively. The average weight on entry of 92.5 kg (204 lb) was reduced to 82.1 kg (181 lb), and the average blood pressure was reduced from 134/83 to 127/79 mm of mercury. The average total cholesterol, LDL-cholesterol, and apolipoprotein B levels at entry of 5.88 mmol per liter (227 mg per dl), 3.92 mmol per liter (152 mg per dl), and 104 mg per dl, respectively, were reduced to 4.45 mmol per liter (172 mg per dl), 2.46 mmol per liter (95 mg per dl), and 79 mg per dl, respectively. Triglyceride levels, however, increased from 2.38 mmol per dl (211 mg per dl) at entry to 2.91 mmol per liter (258 mg per dl) on trial, and HDL-cholesterol levels remained unchanged.

Follow-up angiographic data were not available for one control and six treated subjects. The control subject underwent emergency angiography, with films unsuitable for analysis. One subject in the experimental group died while exercising. One person in the intervention group who had alcoholism dropped out, and four intervention subjects' films were unavailable or unsuitable for technical reasons.

In the available films, 105 coronary artery lesions in the experimental group were compared with 90 in the control group. For the film analysis, computerized quantitative coronary angiography was done at the University of Texas at Houston. End-point analysis was based on the average lesion change; statistical tests of intervention effects on per-subject scores were not reported. The average percentage of diameter stenosed was reduced from 40.0% to 37.8% in the experimental group and increased from 42.7% to 46.1% in the control group, a differential change of 5.6% ($P = .001$). Larger treatment benefit was found in lesions of greater than 50% stenosis at baseline where the differential effect was 8.6% ($P = .03$). All five women in the study (four in the control group) showed evidence of lesion regression. All were postmenopausal, and none were taking estrogens. A per-subject score was constructed from the sign of the average of lesion change scores and found to be indicative of regression in 18 treatment group subjects with 4 in the treatment group showing progression. Among 19 control group subjects, 8 showed regression, 10 progression, and 1 no change.

This trial is the first randomized study reporting regression without drug or surgical therapy to lower blood lipid level. The sustained reduction of LDL-cholesterol levels with life-style change only is remarkable. It supports the findings from the University of California, San Francisco, trial that indicate that women may be better candidates for lesion regression than are men. It also supports the finding in other studies that lesions of greater than 50% stenosis are more likely to respond to treatment.

St Thomas' Atherosclerosis Regression Study

The St Thomas' Atherosclerosis Regression Trial was a three-arm trial assessing the effects of diet and diet plus cholestyramine in reducing plasma cholesterol levels.[22] It was a randomized, controlled end-point-blinded trial. A total of 90 men with coronary heart disease (angina or past myocardial infarction) who had a mean plasma cholesterol level of 7.22 mmol per liter ± 0.76 (SD) (279 mg per dl ± 29.7) were randomly allocated to receive usual care, dietary intervention, or diet plus cholestyramine. Coronary angiography with fully automated quantitative image analysis was repeated after 39 ± 3.5 months in 74

subjects. The mean plasma cholesterol level during the trial period was 6.91, 6.16, and 5.54 mmol per liter, respectively (267, 238, and 214 mg per dl), in controls, diet-treated, and diet-plus-drug-treated subjects.

The proportion of subjects who showed overall progression of coronary artery narrowing (reduced average diameter of coronary artery segments) was significantly smaller in both interventions groups: 15% in the diet group, 12% in the diet plus cholestyramine group, and 46% in the usual-care group. The proportion who showed an increase in average coronary artery segment diameters was 38%, 33%, and 4% respectively, in these groups. The mean absolute width of coronary artery segments decreased by 0.201 mm in the usual-care group, increased by 0.003 mm in diet-treated, and increased by 0.103 mm in diet-plus-cholestyramine-treated subjects ($P < .05$). Changes in coronary artery segmental diameter were independently and significantly correlated with the LDL-cholesterol concentration and the ratio of LDL- to HDL-cholesterol during the trial period. Both interventions reduced the frequency of total cardiovascular events in subjects who did not drop out of the trial.

Several computer-derived end points were also measured, including the percentage of diameter stenosed as used in other trials, minimum segment-width segments, and an index of vessel edge irregularity. It is of considerable interest that the diameter of stenosis showed significant evidence for regression from both treatments in lesions that were greater than 50% stenosed at baseline ($P = .05$) but not in lesions that were 15% to 50% stenosed at baseline ($P = .27$). Both treatments significantly reduced progression in lesions less than 15% stenosed at baseline ($P = .04$).

This study adds to the evidence that dietary change alone that reduces blood total cholesterol levels 15% can retard overall progression and increase the overall regression of coronary artery disease. When diet was augmented by the use of cholestyramine, the reduction in blood cholesterol levels was 24% and coronary benefits were increased. Another important feature is the comparison of lesion response according to baseline severity. This trial confirms the differential treatment effects seen when visible lesions (greater than 15% stenosed) are stratified above and below the level of 50% stenosis. It takes advantage of the increased sensitivity possible with fully automated edge finding to provide information on lesions of less than 15% stenosis. This class of lesions has not received attention because the human panel reading methods used in the NHLBI Type II Study, the Cholesterol Lowering Atherosclerosis Study, and the Program on the Surgical Control of the Hyperlipidemias do not detect them. The same limitation applies to the quantitative procedure used in the Familial Atherosclerosis Treatment Study and the University of California, San Francisco, trials, which depends on humans to trace vessel edges for digitization by a light pen. The Life-style Heart Trial used a method that could have detected changes in these lesions but did not report them. Fully automated computerized evaluations of CLAS films and of the trial of the use of lovastatin (Monitored Atherosclerosis Regression Study)[23] also indicate the substantial effects of baseline lesion status on treatment results.

Conclusions

Together the findings of the controlled clinical trials reviewed here provide convincing evidence that it is possible to reduce the progression and to induce the regression of human atherosclerosis.* Furthermore, from the limited available data, women appear to be more responsive to antiatherosclerosis treatment than men. The degree of change observed in any single lesion with lipid lowering is small compared with what can be accomplished with angioplasty, and there is no selectivity in which lesions will change. The trials have used several different procedures to evaluate coronary artery change, which adds to the overall strength of evidence that atherosclerosis can be modified, but reduces the ability to evaluate the consistency of change across studies. Despite these differences, a theme that emerges from all trials that have made comparisons (the NHLBI Type II, the Familial Atherosclerosis Treatment Study, Life-style Heart Trial, the St Thomas' Atherosclerosis Regression Study, the Monitored Atherosclerosis Regression Study, and CLAS [unpublished]) is that the response to therapy is substantially influenced by the status of lesions at baseline. What is surprising is that the greatest treatment benefits have been in the most severe lesions, those of more than 50% in diameter stenosis at baseline.

A challenge for the future is to reconcile these angiographic trial findings with what we know of the histopathology of atherosclerosis—that is, large lesions have more complicated features than small lesions. Because angiographic trials do not provide information on events within the arterial wall at the level of cell function and deal only with lesions that intrude into the vessel lumen, other methods to track a change in lesions will probably also be needed. As a first step, imaging procedures should be developed that can provide more frequent measurements of plaque status. A second necessary step, until the serial assessment of arterial cell function is possible, will be to correlate serial imaging in animal models with disease structure. This could be done by adding one of several current noninvasive evaluations of wall status, such as magnetic resonance imaging, ultrafast computed tomography, and ultrasound imaging, to animal model experiments. Among these, the least expensive would be ultrasound imaging. None of these procedures would interfere with the traditional practices in animal model atherosclerosis research, such as the killing of test and control animals for histopathologic and cell system studies.

Current theories of atherogenesis suggest a number of targets for intervention to retard lesion progression and foster regression. Two trials not included in this review that tested calcium channel blockade indicate that new coronary artery lesions can be prevented by therapies that may not cause the reversal of early lesions.[24,25] These re-

*See also the editorial by B. G. Brown, MD, "Regression of Atherosclerosis—An Ounce of Prevention," on pages 208-210.

sults, plus growing evidence that relatively early intrusive lesions can be dangerous,[26,27] indicates the need to expand the knowledge of atherosclerosis treatment effects to all stages of the disease. From what we now know of the disease, control through the suppression of early stages of early lesions appears more likely to be feasible than completely preventing the atherosclerotic process.

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Epitomes

Important Advances in Clinical Medicine

Neurology

The Council on Scientific Affairs of the California Medical Association presents the following inventory of items of progress in neurology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome, and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, researchers, and scholars to stay abreast of these items of progress in neurology that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Neurology of the California Medical Association, and the summaries were prepared under its direction.

Reprint requests to Division of Scientific and Educational Activities,
California Medical Association, PO Box 7690, San Francisco, CA 94120-7690

Dysequilibrium in Older People

FALLS IN OLDER PEOPLE are a common source of morbidity and mortality. The risk of falls increases with age after 60 years, and it is greater in women than in men. Most falls in older people result from an accidental slip or trip, often associated with an unsteady gait. The cause of the dysequilibrium can often be traced to decreased sensory input, slowed motor responses, diminished postural reflexes, and weakened support. Sedating medications are a common contributing factor.

Considering the many possible loci of the dysfunction, the examination of older patients complaining of dysequilibrium must include a careful assessment of gait, strength, coordination, reflexes, and sensory function. The broad-based ataxic gait caused by cerebellar disorders is usually readily distinguishable from the milder gait disorders associated with vestibular or somatosensory loss. Furthermore, other cerebellar signs usually accompany cerebellar ataxia. Bilateral vestibular loss may or may not be associated with bilateral hearing loss. A history of ototoxic drug exposure or episodic vertigo is helpful in making a diagnosis, but the only way to document vestibular loss is to do quantitative caloric or rotational testing.

The deterioration of gait that normally occurs with aging must be distinguished from that associated with lesions of the cortical and subcortical motor centers. The shuffling, flexed, steppage gait of Parkinson's disease is often coupled with associated signs, including bradykinesia, cogwheel rigidity, retropulsion, and the characteristic "pill-rolling" tremor. Apraxia of gait, characterized by slow, halting, sliding steps, as if the patient's feet were adhering to the floor, is due to bilateral frontal lobe dysfunction. Common causes include multiple subcortical infarcts, infiltrating tumors, and communicating hydrocephalus. Modern neuroimaging studies readily distinguish these disorders from the nonspecific atrophy seen in patients with a senile gait.

With the exception of those caused by communicating hydrocephalus—which occasionally may be dramatically reversed after the placement of a shunt—inflammatory neuropathies responsive to steroid therapy, and sensory loss due to vitamin B_{12} deficiency, most gait disorders in older people are not reversible. Most patients can be helped by providing support with a cane or a walker, and many benefit from physical therapy with gait training. The use of tranquilizing medications should be scrupulously avoided, as they further impair the central integration of sensory information.

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Molecular Genetics in Neurologic Diseases

GREAT PROGRESS has recently been made in the understanding of the molecular genetics of neurologic disorders that will have a direct effect on the clinical practice of neurology. There are now specific chromosomal assignments for more than 150 diseases primarily affecting the nervous system. Only a few examples can be briefly described here.

Mutations within specific genes have been discovered for Duchenne muscular dystrophy on the X chromosome, in the amyloid precursor protein gene on chromosome 21 in early-onset familial Alzheimer's disease, in the neurofibromatosis type 1 gene on the long arm of chromosome 17, and in an area on the short arm of chromosome

17 that includes a peripheral myelin protein gene related to the most common form of Charcot-Marie-Tooth hereditary neuropathy. Genetic linkage evidence has also demonstrated the existence of another, as yet unidentified, gene for early-onset familial Alzheimer's disease on chromosome 14. Other gene locations of interest include those of facioscapulohumeral muscular dystrophy on chromosome 4, infantile spinal muscular atrophy on chromosome 5, Friedreich's ataxia on chromosome 9, tuberous sclerosis on chromosome 16, and the prion protein on chromosome 20. Recently the gene for Huntington's disease on the short arm of chromosome 4 has been identified after a persistent ten-year search.

Several disorders have been associated with variable and unstable repeats of DNA triplets that may expand to great lengths. These expansions are related to unusual inheritance patterns, including the phenomenon of anticipation (the worsening of a clinical syndrome with each new generation). These disorders include myotonic muscular dystrophy, fragile X mental retardation, and Kennedy's X-linked bulbospinal muscular atrophy. A similar phenomenon has been noted in Huntington's disease.

Direct DNA diagnostic tests are commercially available for Duchenne type and myotonic muscular dystrophies and will soon be available for the most common form of type 1 Charcot-Marie-Tooth neuropathy with slow nerve-conduction velocities. Efforts are underway to make a direct DNA test available for Huntington's disease. Indirect DNA genetic linkage studies can be done for the presymptomatic diagnosis of those disorders in which closely linked markers have been identified (for example, Friedreich's ataxia and infantile spinal muscular atrophy). These indirect studies always have an error rate of 1% to 5% and require blood specimens from many family members.

Mitochondria have their own DNA separate from nuclear DNA and are specifically involved with the respiratory chain and oxidative phosphorylation. Mitochondrial DNA is inherited from the cytoplasm of dividing cells and not from the nucleus. Mutations of mitochondrial DNA have been discovered in a wide range of neurologic syndromes presenting as either sporadic cases or inherited conditions passed only through affected women (sperm does not contain mitochondrial DNA). These diseases include Kearns-Sayre progressive external ophthalmoplegia with retinopathy, Leber's hereditary optic neuropathy, myoclonic epilepsy with ragged red fibers, and mitochondrial encephalomyopathy with lactic acidosis and stroke. Screening tests using blood or muscle biopsy specimens for many of these mitochondrial diseases are also now commercially available.

Detailed and accurate counseling for all genetic disorders continues to be important. The patients and families must be educated about the risks of inheritance, the prognosis, and the variability of symptoms and complications. The accuracy and vagaries of the individual tests must be understood. Implications for employment, family planning, and insurance need to be assessed. Finally, the idea of identifying carriers of serious untreatable, progressive neurologic disorders decades before symptoms occur is a new concept for physicians and patients that will require continuing accommodation and assessment.

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Radiosurgical Treatment of Brain Lesions

THE ASSOCIATION OF STEREOTACTIC SURGERY with radiant energy to cause discrete lesions in the brain for the control of functional disorders and intractable pain led to the idea of radiosurgery. But the inability to confirm the radiosurgical target led to the procedure's falling into disuse for the surgical treatment of functional neurologic disorders. Its use was restricted to the treatment of arteriovenous malformations and pituitary tumors that could be precisely targeted using angiography and pneumoencephalography. Radiosurgical applications have expanded immensely since computed tomographic images and computer calculation of radiation distribution became available.

The modern definition of radiosurgery is that of a noninvasive technique in which image manipulation and high doses of radiant energy are used to destroy lesions in the brain with surgical precision. Two forms of radiant energy have been used, particulate (proton beam or helium beam) and electromagnetic (cobalt 60, linear accelerators). No significant radiobiologic difference has been established between these two forms. The natural decay of ^{60}Co produces the gamma rays used as a source of energy for the commercially available radiosurgical instrument known as the "gamma knife." Linear accelerators artificially produce a photon beam that can be precisely focused to a target using stereotactic techniques.

Radiosurgery is effective for the treatment of arteriovenous malformations 3 cm in diameter or smaller. Total arteriovenous malformation obliteration occurs in 80% of cases within two years. Larger arteriovenous malformations can be palliated with radiosurgery, with total obliteration in 50% of the cases. Radiosurgery can halt the growth of acoustic neuromas in more than 80% of the cases. It has been established as part of multimodality treatment for the effective control of solitary and multiple metastatic lesions to the brain, with a success rate of more than 80%.

The risks of radiosurgery are small and are related to radiation necrosis. Edema surrounding the treated lesions may cause transient neurologic deficits. Meticulous ste-

reotactic technique and the judicious determination of the radiation dose are key factors in decreasing the complication rate.

Because radiosurgery is a new technology, it is still considered a secondary choice to the resection of lesions of the brain. But its proven effect, noninvasive nature, and cost-effectiveness—it is usually done on an outpatient basis—will make this technique more and more a part of the treatment of brain lesions.

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Ticlopidine Hydrochloride and Prevention of Stroke

TICLOPIDINE HYDROCHLORIDE is a novel platelet antiaggregant agent now available in the United States as an alternative to aspirin for the secondary prevention of stroke. Unlike aspirin, ticlopidine and other thienopyridine compounds have no effect on cyclooxygenase. Specific mechanisms of action remain under investigation, but likely involve the inhibition of adenosine diphosphate signal transduction at the platelet membrane. Ticlopidine provides greater efficacy than aspirin, but at the expense of more substantial adverse effects.

The Ticlopidine Aspirin Stroke Study directly compared these agents in subjects with recent transient ischemic stroke or mild ischemic stroke (cerebral or retinal) and found a 21% relative risk reduction in stroke (intention-to-treat analysis) with ticlopidine, 250 mg twice a day, versus aspirin, 650 mg twice a day. Benefits of ticlopidine use were shown in both sexes, with a three-year relative risk reduction in stroke of 27% for women and 19% for men. Notably, the advantage of ticlopidine use was greatest during the initial year: stroke recurrence was nearly halved compared with aspirin treatment.

Meta-analysis of all placebo-controlled aspirin trials before 1988 provides an estimated stroke risk reduction of 22% in subjects with a previous transient ischemic attack or minor stroke. These protective effects of aspirin can probably be generalized to women and to persons who have had a substantial stroke. The evidence for its efficacy in women is not extensive, however, and no large trials have evaluated the use of aspirin for preventing secondary stroke exclusively following a completed stroke. The Canadian American Ticlopidine Study, a placebo-controlled trial in subjects with recent thromboembolic stroke, showed a 33.5% stroke risk reduction during the first year in women and men receiving ticlopidine. Efficacy analysis also revealed a 30.2% risk reduction with ticlopidine use for combined stroke, myocardial infarct, and vascular death.

Most side effects of ticlopidine use—diarrhea, dyspepsia, rash—are minor, but lead to medication cessation in about one of five subjects. Serum cholesterol levels may increase slightly, but this occurs in patients with a reduced incidence of stroke, myocardial infarct, and vascular death. Although bleeding time is prolonged, serious hemorrhage is uncommon and gastrointestinal bleeding less common than with 1,300 mg per day of aspirin. The major adverse effect of ticlopidine use is a severe, reversible neutropenia (less than 450×10^3 neutrophils per liter) occurring in nearly 1% of patients, with onset virtually always during the first three months of therapy. Complete blood counts must be obtained every two weeks during the first three months of treatment. In the Ticlopidine Aspirin Stroke Study, the incidence of serious adverse effects did not differ between groups. Nevertheless, only reliable persons who understand the risks of ticlopidine should be considered treatment candidates.

The benefits of ticlopidine therapy are greatest for the first year after a transient ischemic attack or stroke, when the risk of recurrent stroke is highest. The use of ticlopidine should be considered on an individual basis in women and men at high risk for noncardioembolic ischemic stroke, especially those with a recent transient ischemic attack or completed stroke. In addition, ticlopidine use is indicated in persons who are intolerant to aspirin or who have recurrence of cerebral ischemia while on aspirin prophylaxis.

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Magnetic Resonance Spectroscopy

MAGNETIC RESONANCE SPECTROSCOPY (MRS), a noninvasive method to measure metabolites in brain tissues, has been used to study the abnormalities of stroke, multiple sclerosis, dementia, and encephalopathy.

The basis of nuclear magnetic resonance spectroscopy is that certain atomic nuclei have weak magnetic moments that align in the direction of a strong magnetic field. These nuclei can be manipulated in the magnet to yield information about their anatomical position or biochemical structure. Hydrogen protons in water have resonance properties that allow them to form images in magnetic resonance imaging (MRI). Hydrogen 1 and phosphorus 31 are the two major nuclei with magnetic

moments that have been used in MRS studies of people. Magnetic resonance spectroscopy using ^{1}H is done with suppression of the large signal from water molecules (about 55 mol per liter) so that the protons in other molecules that are present in lower concentrations (1 mmol per liter or more) can be detected. Using ^{31}P, MRS allows the detection of phosphorus in adenosine triphosphate (ATP), phosphocreatine, and membrane phospholipids. It has been used to measure energy substrates, ATP and phosphocreatine, and pH in muscle diseases. One of the first applications of MRS to a human disease, McArdle's disease, a muscle disorder with a metabolic defect in glycogen metabolism, failed to show a normal fall in pH due to lactate accumulation during exercise. Subsequent studies with ^{31}P-MRS have shown abnormalities in pH and metabolites in a number of muscle disorders.

The first application of MRS to the study of brain tissue in humans was also done with ^{31}P-MRS. Infants with anoxic encephalopathy were shown to have decreased energy substrates, which correlated with the extent of injury. Studies in patients with stroke have shown an initial acidosis due to the build-up of lactate and other proton donors in the ischemic tissue. After several days, however, there is tissue alkalosis. This flip-flop of acidosis to alkalosis has been recorded with ^{31}P-MRS and the degree of alkalosis shown to relate to the severity of the infarct. Energy substrates are depleted in the infarcted tissue, but the loss of ATP is a late event, indicating irreversible death of the cells.

Proton MRS has shown early biochemical changes in infarcted brain tissue. The proton spectrum has a large peak from *N*-acetylaspartate, which is mainly found in neurons. The *N*-acetylaspartate signal is preserved early in infarction. It then begins to fall, suggesting that there is a window when cells remain viable and amenable to treatment. Lactate appears in the ^{1}H-MRS spectrum during the acute phase of an infarct.

Other diseases have begun to be studied with MRS. In Alzheimer's disease, a defect in membrane phospholipids has been shown by ^{31}P-MRS. Multiple sclerosis plaques have been shown by ^{1}H-MRS to have a loss of *N*-acetylaspartate in the chronic stage and an increase in lipid signals and choline in the acute stage. Hepatic encephalopathy produces changes in ^{1}H-MRS spectra in the glutamine or glutamate region. Epileptogenic foci have been localized with ^{31}P-MRS.

Magnetic resonance spectroscopy can be done as part of a routine MRI on commercially available MRI instruments in less than an hour. Although it provides unique biochemical information on brain metabolites and is useful in assessing the extent of tissue injury, further studies will be needed to determine its role in diagnosing and planning treatment in neurologic diseases.

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Outcomes Research—Possible Effects on Clinical Practice

OVER THE PAST TWO DECADES, there has been a great expansion in neuroscientific knowledge and techniques that are expected to improve the health of patients with neurologic disease. This research has focused on the molecular basis of disease and is expected to result in new therapies, such as transplantation, growth factors, and gene therapies. Expectations are high for the eventual incorporation of the fruits of this research into the clinical practice of neurology.

Along with these advances, growing concern about escalating health care costs has stimulated research into how to identify health care practices that are most cost-effective yet most efficient. Although randomized controlled trials provide the most rigorous data on efficacy—benefit under the best possible circumstances—evidence of efficacy does not necessarily mean that a procedure or treatment will be effective outside the trial setting. The high cost and time requirements of randomized controlled trials also prevent using them for evaluating a large number of treatments or procedures. Finally, results of these trials may not be generalizable to many patients because of exclusion criteria for the trials.

A proposed method for addressing this problem is "outcomes research," so called because of its emphasis on measuring clinically relevant health outcomes. These include not only disease symptoms and mortality, but also daily functioning and activities, emotional well-being, and other dimensions of health-related quality of life. Other features of outcomes research are the use of observational studies, that is, data collected from nonexperimental studies, with careful adjustment for case mix and other possible confounding variables; the use of relatively large data bases (some have advocated that all patient visits be entered into a data base to evaluate outcomes); the use of quantitative techniques to analyze the existing medical literature; and the incorporation of patient preferences for different health outcomes in making clinical decisions. To date, two large-scale federally funded outcome studies have been undertaken to evaluate neurologically relevant conditions: low back pain and stroke prevention. A smaller outcome study of epilepsy surgery and an effort to develop clinical guidelines for rehabilitation after stroke using quantitative literature review and expert panel consensus are also in progress.

What are the mechanisms by which this growth in outcomes research may affect the clinical practice of neurology (and other specialties)? The first is by educating practicing physicians. This can be accomplished through the journal publication of meta-analyses and

other outcome study results, continuing medical education courses, and developing and distributing clinical "guidelines" to practitioners (an ongoing venture of the Quality Standards Subcommittee of the American Academy of Neurology, the federal government's Agency for Health Care Policy and Research, and other organizations).

A second approach is through formal medical education. Much greater emphasis could be given to educating students and residents to treat patients using "evidence-based medicine"—that based on the quantitative evaluation of the results of published studies. At least one effort to implement this approach is underway at a Canadian medical school.

The third mechanism is by government changes in health policy. This may occur through changes in Medicare or Medicaid reimbursement policies. For example, payers might decide to link reimbursement for an electroencephalogram to clinical situations in which outcomes research indicates a possible health benefit from the test. As a second example, some outcomes research has shown that changing the informed consent process to facilitate patient participation in decision making can result in a different pattern of patient decisions about treatment. Such changes in the decision-making process could be made mandatory, particularly for long-term conditions in which alternative therapies differ negligibly in how they affect disease progression yet have different effects on health-related quality of life.

Finally, the current health care delivery system and the technologies that it uses could be revised by the results of outcomes research. Certainly in the ongoing efforts toward containing costs, any new diagnostic technology or therapy will be scrutinized more closely and will probably be subjected to more regulation than in the past, with the requirement that its cost-effectiveness be documented before its widespread use.

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Alerts, Notices, and Case Reports

Hyporeninemic Hypoaldosteronism Complicating Primary Autonomic Insufficiency

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THE SYNDROME OF hyporeninemic hypoaldosteronism occurs in a heterogeneous group of clinical disorders in which a nephropathic process is usually present with mild to moderate renal insufficiency.[1-3] The commonest renal disease to produce hyporeninemic hypoaldosteronism is diabetic nephropathy, but other renal disorders may also produce it. Rarely, no intrinsic renal disease is found.[3] Hyperchloremic metabolic acidosis and hyperkalemia are usually present in this disorder, and the name "type IV renal tubular acidosis" has been applied.[4] Possible causes for hyporeninemia in this syndrome include inadequate renin release or the conversion of prorenin to renin.[1-5]

The sympathetic nervous system is a major regulator of renin production in the kidneys.[6] β-Adrenergic nerve terminals directly stimulate renin release from juxtaglomerular cells; systemic β- and α-adrenergic hormones cause renin release by stimulating prostacyclin production by renal endothelial cells.[7,8] Prostacyclin is thus a major regulator of renin production.

Autonomic failure with reduced sympathetic nervous system postural responses may also cause this disorder.[9,10] Plasma norepinephrine released from postganglionic sympathetic terminals[11] regulates renal prostacyclin release,[12] which activates renin from prorenin or promotes renin release.[7,8] The reduced circulating norepinephrine levels encountered in autonomic insufficiency is thus a possible explanation for hyporeninemia.

We report a case of severe hyporeninemic hypoaldosteronism associated with autonomic insufficiency. This syndrome occurred in a patient who had neither diabetes mellitus nor other nephropathy and who had a normal creatinine clearance. The patient had neither hyperkalemia nor metabolic acidosis despite severe hyporeninemia and mineralocorticoid deficiency. Urinary and plasma aldosterone and plasma renin activity under both basal and stimulated conditions was low when compared with the activity recorded in other patients with the disorder, with or without associated autonomic failure.[1-3,9,10] Recurrent orthostasis and syncope, reduced plasma norepinephrine levels with the patient upright, and decreased renal prostacyclin excretion were documented. The low catecholamine production was proposed to play a role in the patient's hyporeninemia. No intrinsic renal disease was clinically apparent. Apart from orthostatic hypotension, no other manifestations of autonomic insufficiency were present.

Plasma levels of aldosterone and its steroid precursors in this patient following postural and volume-depleting stimulation suggested reduced activity of corticosterone methyloxidase. This enzyme in the zona glomerulosa of the adrenal gland catalyzes the terminal steps of aldosterone biosynthesis; it is sensitive to angiotensin II control.[13,14]

Supplementation with fludrocortisone acetate abolished the patient's orthostatic symptoms, consistent with the syndromes of both autonomic failure and hypoaldosteronism.

Report of a Case

The patient, a 20-year-old man, was admitted to St Elizabeth Hospital Medical Center (Youngstown, Ohio) in October 1990 because of orthostatic dizziness for three to four months, particularly severe during the week before admission. His medical and family histories were otherwise normal. The patient used no medication. On physical examination on admission, no abnormalities were elicited except for postural blood pressure changes, with dizziness. His supine blood pressure was 95/60 mm of mercury. When he stood upright, his blood pressure dropped to 60/42 mm of mercury, and there was a rise in his heart rate from 60 to 90 beats per minute.

On admission an electrocardiogram revealed sinus rhythm with an early repolarization variant. Chest x-ray films and computed tomography of the brain were normal; cerebral angiography showed a small venovenous hemangioma but was otherwise normal.

Admission laboratory tests revealed a normal complete blood count and coagulation profile. A sickle cell preparation was negative. Serum electrolyte values were as follows: sodium 141, potassium 4.1, chloride 106, and bicarbonate 31 mmol per liter; blood urea nitrogen, 2.8 mmol per liter (normal, 3.0 to 6.5); and plasma creatinine, 88 mmol per liter (normal, 50 to 110). Arterial blood gas measurements with the patient breathing room air showed a pH of 7.42, P_{CO_2} 37 mm of mercury, P_{O_2} 97 mm of mercury, and bicarbonate 26 mEq per liter. Tests of hepatic function gave normal values.

A 24-hour creatinine clearance was 2.33 ml per second (140 ml per minute), and a 24-hour urine protein level was 0.12 grams per day (120 mg [52 mg per gram of creatinine]). The urinary sediment did not contain inflammatory cells, epithelial cells, or casts. Ultrasonog-

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raphy of both kidneys revealed normal size and architecture.

Other chemistry values included a random blood glucose of 5.0 mmol per liter (90 mg per dl; normal, 3.9 to 6.1) and a glycosylated hemoglobin of 0.054 (5.4%; normal, 0.04 to 0.07). Tests of thyroid function showed a normal total serum thyroxine level, triiodothyronine resin uptake, free thyroxine index, and thyroid-stimulating hormone level. The plasma testosterone level was 30.1 nmol per liter (normal adult male, 14.0 to 28.0). Intact parathyroid hormone and total and ionized serum calcium levels (arterial pH corrected) were all normal.

Pituitary-adrenal axis testing showed the following values: AM (0700) and PM (1600) baseline adrenocorticotropic hormone (ACTH) levels were 41 pmol per liter (normal, 4 to 22) and 2 pmol per liter, respectively. AM and PM baseline plasma cortisol levels were 375 nmol per liter (normal, 110 to 520) and 47 nmol per liter (normal, 50 to 410), respectively. One-hour ACTH stimulation (40 U of cosyntropin given intravenously) gave a plasma cortisol level at 0700 to 0800 of 306 nmol per liter, increased to 491 nmol per liter; 24-hour ACTH stimulation (100 U of cosyntropin given intravenously) gave a plasma cortisol level at 0700 to 0700 of 179 nmol per liter, increased to 1,349 nmol per liter. A 24-hour ACTH-stimulated 17-hydroxycorticoid excretion value was 152 μmol. All results were within a normal physiologic range,[15(p2662)] except the AM plasma ACTH level, which was elevated; the reason for this was unclear.

To evaluate the renin-aldosterone axis and mineralocorticoid production in this patient, renin-sodium-aldosterone profiling was carried out,[16] followed by the postural stimulation of his renin, aldosterone, and mineralocorticoid reserve (Table 1). After a two-day period of moderate sodium restriction (80 mEq per 24 hours) plus approximately 60 to 80 mEq per day of dietary potassium with ad lib in-hospital activity, 24-hour urinary electrolyte measurements, 24-hour urine aldosterone excretion rate, and early AM plasma renin activity with the patient supine were measured, the last following a 12-hour fast. The patient was given 80 mg of furosemide orally followed by a continuous five-hour period of standing upright and walking. At the conclusion of this five-hour period, tests of plasma renin activity were repeated, and plasma deoxycorticosterone, corticosterone, 18-hydroxycorticosterone, and aldosterone levels were measured (Endocrine Sciences Laboratories, Calabasas Hills, California). During the five hours of ambulation, the patient's blood pressure dropped from 110/80 to 90/60 mm of mercury without notable symptoms. As shown in Table 1, there was a pronounced suppression of the 24-hour aldosterone excretion rate, supine and upright plasma renin activity, upright plasma 18-hydroxycorticosterone, and plasma aldosterone levels.

To further evaluate this patient's syncope, a standardized tilt-table examination was done to exclude vagally mediated syncope; the results were normal.[17] The patient's upright stimulated plasma norepinephrine level (30 minutes of standing) was reduced, however, to 2.5 nmol per liter[11,18]; upright plasma epinephrine and plasma dopamine levels were also suppressed (both to < 70 pmol per liter). Pressor responses to exercise and exogenous norepinephrine to further assess autonomic failure were not tested because of patient noncompliance. The patient also declined a rectal or fat biopsy to evaluate for amyloidosis. Renal prostacyclin production, measured as the urinary excretion of 6-keto-prostaglandin-$F_{1\alpha}$, was 92 ng per gram of creatinine (193 ng per 24 hours); this was lower than normal.[12] Urinary prostaglandin E_2 and thromboxane B_2 excretion was normal, 52 ng per 24 hours and 388 ng per 24 hours, respectively (Interscience Institute Laboratories, Inglewood, California).[19]

After discharge the patient was given fludrocortisone acetate, 0.2 mg twice a day. On several return visits his blood pressure consistently remained between 110 and 120 mm of mercury systolic, and he reported no further orthostatic symptoms.

Multiple electrolyte measurements, both on and off exogenous mineralocorticoid, revealed normal serum levels of sodium, potassium, chloride, and plasma bicarbonate.

Discussion

As seen in Table 1, this patient had severe hyporeninemic hypoaldosteronism, with low baseline plasma renin

TABLE 1.—*Renin-Sodium-Aldosterone Profiling and Mineralocorticoid Synthesis in Hyporeninemic Hypoaldosteronism**

	Urinary Excretion Rate/24 hr			*Plasma Mineralocorticoid Hormone Levels*				
Day	*Sodium, mEq*	*Potassium, mEq*	*Aldosterone, μg*	*Renin Activity, ng/ml/hr*	*Deoxycorticosterone, ng/dl*	*Corticosterone, ng/dl*	*18-Hydroxycorticosterone, ng/dl*	*Aldosterone ng/dl*
1	80	22	<1 (8-24)†	--	--	--	--	--
2	--	--	--	0.1 (1.8-6.2)†‡	--	--	--	--
2	--	--	--	0.3 (13-23)§	9.9 (2-19)§	448 (130-820)§	14 (19-128)§	<1 (7-42)§

*Protocol details are given in the text.

†The numbers in parentheses are reference ranges normalized to a 24-hour urine sodium value of 80 mEq (from Laragh et al[16]).

‡Patient values while the patient was supine.

§Patient values after the administration of furosemide, 80 mg, and after the patient was upright and ambulatory for 5 hours. (The numbers in parentheses are expected values [from Laragh et al,[16] Patrono et al,[19] and Sowers et al[24]].)

activity and no increase following moderate salt restriction, upright posture, and the administration of furosemide.

The 24-hour urinary aldosterone excretion and plasma aldosterone level following the same provocative tests were markedly suppressed. This is, therefore, a clear case of hyporeninemic hypoaldosteronism, occurring in the absence of renal parenchymal disease—cystic, glomerular, or tubulointerstitial—that might lower renin production.[1-3] Without apparent renal parenchymal disease, extrarenal factors were studied for causes of low plasma renin activity. Features favoring autonomic insufficiency as the cause of the disorder in this patient were recurrent hypotension and syncope and blunted norepinephrine release following 30 minutes in an upright position.[20] Although no parasympathetic dysfunction (anhidrosis or genitourinary or gastrointestinal symptoms) was present, this does not exclude autonomic insufficiency.[18,20]

The patient's normal acid-base and electrolyte values are unusual in hyporeninemic hypoaldosteronism, which usually causes a normal anion-gap metabolic acidosis and hyperkalemia.[4,21] The absence of hyperkalemia and the resulting preservation of ammonia production[4] partially defended the patient's acid-base state; normal renal function and normal production of acid-secreting steroid hormones apart from aldosterone[22] also probably helped the patient to achieve normal acid excretion and balance.

The patient had normal basal and ACTH-stimulated glucocorticoid production and normal mineralocorticoid synthesis through the precursor steroids deoxycorticosterone and corticosterone, but he had reduced 18-hydroxycorticosterone and aldosterone biosynthesis, consistent with previous reports of this disorder.[23,24] Angiotensin II regulates overall mineralocorticoid synthesis in the zona glomerulosa through the control of corticosterone methyloxidase (classes I and II).[13] This enzyme system controls the production of 18-hydroxycortisone and aldosterone.[14] In low renin states, a reduction in levels of angiotensin II-regulated products would be expected. After postural and diuretic stimulation, this patient had normal deoxycorticosterone and corticosterone levels, whereas the plasma 18-hydroxycorticosterone level was reduced and aldosterone, the final product of corticosterone methyloxidase type II, was totally undetectable. Thus, the overall activity of the corticosterone methyloxidase system in this patient was substantially reduced, consistent with deficient renin-angiotensin II signaling of the adrenal cortex.

The patient excreted 80 mEq of sodium per 24 hours while still showing orthostatic hypotension. Although this represents sodium balance on an inpatient diet, it still suggests inappropriate sodium wasting. Both proximal and distal renal sodium reabsorption are dependent on the components of the renin-angiotensin-aldosterone system. Thus, both mechanisms were probably impaired in this patient, contributing to an ongoing sodium imbalance, reduced plasma volume, and sodium-mediated pressor sensitivity.[25]

In summary, though not rigorously proved, this patient probably had primary autonomic insufficiency, based on the clinical presentation and plasma catecholamine levels while the patient was upright. The severe impairment of renin and aldosterone production implies that renal parenchymal disease is not required to produce hyporeninemic hypoaldosteronism. Indeed, normal renal function with primary autonomic insufficiency, as in this patient, may protect against the electrolyte and acid-base consequences otherwise expected with this disorder.

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Encephalopathy Due to Severe Hyponatremia in an Ultramarathon Runner

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ACUTE HYPONATREMIA has been noted in some athletes after they participated in endurance exercise. Although the ingestion of hypotonic fluid combined with sodium chloride losses in sweat has been most commonly implicated as the cause of this syndrome, its pathogenesis is unclear because of fragmentary laboratory data. We present a case of severe hyponatremia with life-threatening encephalopathy that developed in an ultramarathon runner after he dropped out of a race because of foot blisters. The patient showed clear evidence of volume expansion and had a documented abnormality in urinary dilution. We postulate that much of the ingested water was absorbed only after he discontinued exertion and was retained because of the continued secretion of antidiuretic hormone (ADH). The ingestion of a nonsteroidal anti-inflammatory drug before the marathon may have exacerbated the urinary defect in dilution.

Report of a Case

The patient, a 57-year-old man, came to medical attention after a seizure occurred one hour after he completed 88.5 km (55 mi) of a 161-km (100-mi) ultramarathon. The patient had previously been in excellent health. He had taken ibuprofen for several days to relieve mild arthralgias, but was taking no other medication. His weight at the start of the race was 72 kg. During the race he drank 12 liters of a glucose and water solution. After running 64 km (40 mi), his weight was 74 kg. He dropped out at 88.5 km because of severe blisters on both feet. Approximately 45 minutes later, he became confused and disoriented, his speech became slurred, and he had a generalized seizure. In the emergency department his temperature was 36°C (96.8°F), his pulse was 69 beats per minute, blood pressure 146/86 mm of mercury, and respirations 14 per minute. He had decorticate posturing. His optic discs were flat, pupils were equal and reactive to light, and corneal reflexes were present. Deep tendon reflexes were brisk and symmetric, and Babinski's sign was present on both sides. The patient withdrew to deep pain but did not localize to voice or follow commands. His neck veins were distended to the angle of the jaw. There were no clinical signs of dehydration. Blisters were present on both feet. The physical examination otherwise showed no abnormalities.

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ABBREVIATIONS USED IN TEXT

ADH = antidiuretic hormone
ECF = extracellular fluid volume

Initial laboratory tests elicited the following values: hematocrit, 0.38; serum electrolytes: sodium, 119, potassium, 3.6, and chloride, 89 mmol per liter; total carbon dioxide, 13 mmol per liter (13 mEq per liter); urea nitrogen, 5 mmol per liter (14 mg per dl); creatinine, 100 μmol per liter (1.1 mg per dl); glucose, 8.1 mmol per liter (146 mg per dl); osmolality, 248 mmol per kg of water. Urine osmolality was 474 mmol per kg of water and urine sodium, 39 mmol per liter. Arterial blood gas results with the patient breathing 2 liters of oxygen by nasal cannula were pH 7.43, P_{CO_2} 4.5 kPa (34 mm of mercury), and P_{O_2} 16.0 kPa (120 mm of mercury). The electrocardiogram showed sinus rhythm with a rate of 75 per minute; nonspecific ST and T-wave abnormalities were present. A chest x-ray film and a noncontrast computed tomographic scan of the head were normal. After the patient returned from the computed tomographic scan, anisocoria was noted, with the right pupil 6 mm and the left pupil 2 mm; both pupils reacted sluggishly to light. The serum sodium was again measured and was 111 mmol per liter.

Furosemide, mannitol, and a 3% solution of saline were administered intravenously. Twelve hours after admission the patient remained obtunded, although the anisocoria had resolved. The serum sodium level was 125 mmol per liter. On the second hospital day, the patient was somnolent but would localize to voice. Over the next four days, he gradually recovered and was discharged.

Discussion

Hyponatremia is an underrecognized complication of endurance exercise. Hiller and co-workers reported that 19 of 64 (30%) finishers in the 1984 Hawaiian Ironman triathlon had an abnormally low postrace serum sodium concentration.[1] Noakes and associates described the development of hyponatremic encephalopathy in four athletes during endurance events lasting longer than seven hours.[2] Urine osmolality was increased in the one patient for whom this value was reported. More recently, Frizzell and colleagues described the development of hyponatremic encephalopathy in two runners competing in the 1983 American Medical Joggers Association ultramarathon race.[3] No values for urine sodium or osmolality were reported for either patient.

Our patient presented with acute hyponatremic encephalopathy and had clinical and laboratory findings consistent with water intoxication.[4] The severe hyponatremia was not associated with clinical evidence of volume depletion. The patient had gained 2 kg in weight and did not have tachycardia or hypotension. In fact, his vascular volume seemed to be increased based on the finding of neck vein distention. In addition, he was excreting sodium in his urine despite severe hyponatremia. The

urine osmolality and sodium concentration were consistent with ADH effects despite his apparent volume-expanded state.

An intriguing aspect of this disorder is the time course of symptoms and hyponatremia. The patient was asymptomatic until almost an hour after he stopped running, and his serum sodium level fell from 119 to 111 mmol per liter during the first hour of hospital admission without his receiving any hypotonic fluids. Splanchnic ischemia, which may impair enteral absorption, can occur during endurance exercise.[5] It is possible, therefore, that part of the water ingested by our patient was not absorbed while he was running. With the cessation of exercise and reperfusion of the splanchnic bed, this sequestered water could have been absorbed rapidly, worsening his hyponatremia and expanding his body fluid volume. Although this seems a likely explanation for the abrupt fall in his serum sodium level, continued ADH secretion is required for the absorbed water to be retained.

Hyponatremia after endurance exercise has been attributed to sodium and water losses in sweat and replacement with water.[2,5] According to this view, urinary water retention results from ADH secretion stimulated by a reduction in extracellular fluid (ECF) volume occurring as a consequence of sodium loss. If this construction is correct, the urine sodium concentration should be vanishingly low. In this patient, however, the urine sodium level of 38 mmol per liter was consistent with the evidence on physical examination of a normal or increased ECF volume. It is possible that the physical stress of endurance exercise results in continued ADH secretion after the cessation of exercise, even when the ECF volume is expanded and hyponatremia is present. Various stresses including pain, hypoxia, hypercapnia, and hypoglycemia have been associated with ADH secretion and hyponatremia.[4] Clearly more work needs to be done to characterize the factors responsible for this syndrome. Our patient had been taking ibuprofen, a prostaglandin inhibitor. Severe hyponatremia has been reported with the use of this class of drugs,[6,7] presumably because prostaglandin is a normal antagonist to the hydroosmotic effect of ADH. Whether this drug was a contributing factor in the development of hyponatremia in our patient is unknown.

The treatment of hyponatremia with an isotonic or hypertonic saline solution is critically important when notable encephalopathy is present.[4,8,9] If there is evidence of ECF volume expansion, furosemide is a useful therapeutic adjunct through its effect of reducing the ECF volume and allowing the subsequent retention of administered sodium.[10] Its use can be hazardous, however, if the ECF volume is reduced. An improved understanding of the role of sodium chloride loss, fluid replacement, and ADH secretion in this life-threatening complication of ultramarathon competition is needed to develop a rational approach to treatment and, more important, to prevent its development. Given the findings in one patient, we recommend that athletes be cautioned regarding the overzealous ingestion of water during endurance exercise. They should also be cautioned about the possible effects of nonsteroidal anti-inflammatory drugs on renal function and urinary dilution.

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Use of Aprotinin to Reduce Intraoperative Bleeding

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BLEEDING DURING a surgical procedure is a common problem associated with both morbidity and death of surgical patients in the United States; it increases the risk of multisystem organ failure and death. Transfusion therapy is associated with the additional risks of allergic reaction and the transmission of infectious diseases such as hepatitis and the acquired immunodeficiency syndrome. Despite tremendous advances in blood banking, public concern about the safety of America's blood supply has substantially increased the fear of transfusion for many patients having surgical treatment.

The use of aprotinin, a serine protease inhibitor, has been shown recently to reduce dramatically the blood loss in operations that involve cardiopulmonary bypass and in other cardiac operations.[1-7] Several of the studies showing efficacy and safety have been randomized, placebo-controlled trials.[1-4,6] The drug is now used extensively in Europe and the Middle East for cardiac surgery. Although the mechanism of action has not been clearly established, it appears that aprotinin improves platelet function, which is impaired following cardiopulmonary bypass.[7,8] Apro-

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ABBREVIATIONS USED IN TEXT

HIV = human immunodeficiency virus
KIU = kallikrein-inhibiting unit

tinin may also decrease fibrinolysis.[7,9] Clinical trials are currently underway in the United States to obtain approval for the use of the drug during operations that involve cardiopulmonary bypass.

Aprotinin has also been used to decrease blood loss in operations that do not require cardiopulmonary bypass.[10-17] It has been used during orthotopic liver transplantation, substantially reducing the transfusion requirement and intensive care unit stays for treated patients.[10-13] It has also been used in neurosurgery, orthopedic surgery, gynecologic surgery, urologic surgery, and plastic surgery.[7,14-19] Reports evaluating its effectiveness in these types of operations come mostly from Germany where it has been used for many years in various surgical procedures.[14] The use of aprotinin in patients having noncardiac operations outside the United States is not uncommon despite a lack of large, carefully controlled clinical trials.

Noncardiac surgical procedures that place patients at an increased risk of bleeding include major orthopedic reconstructions of the back for scoliosis; frequently intraoperative transfusion is required, and in some cases the amount of bleeding can be life threatening. Patients positive for the human immunodeficiency virus (HIV) who have excessive bleeding during a surgical procedure place operating room staff at an increased risk of exposure to HIV during the procedure. In this report we describe the case of a woman with severe scoliosis who suffered massive hemorrhage during a back reconstruction in 1982. During treatment of that hemorrhage, she acquired HIV. When she presented for a second major back reconstruction in 1992, she was treated with aprotinin, resulting in minimal blood loss.

Report of a Case

The patient, a 31-year-old woman, was born prematurely and was diagnosed as having cerebral palsy at about 6 months of age. At the time of her first admission for back correction, she had a prominent spastic diplegia. She had severe scoliosis with a double major curve and back pain and, at age 21 years, entered Stanford University Medical Center (Palo Alto, California) for fixation. Under general anesthesia with halothane, nitrous oxide, and pancuronium bromide, she underwent a Luque rod fixation of the posterior spine from T-4 to the pelvis. After the first hour of the procedure, she had lost about 17% of her estimated blood volume, and hypotensive anesthesia was begun by adding sodium nitroprusside to keep her mean arterial pressure between 60 and 65 mm of mercury. Despite this measure she continued to bleed excessively, and by the end of her 12-hour surgical procedure her estimated blood loss was more than 9 liters. She was transfused with 18 units of blood, 8 units of fresh frozen plasma, 16 units of platelets, 6 liters of a normal saline solution, and an unstated amount of cell-saver blood. She was transferred to the intensive care unit, intubated, and placed on full mechanical ventilation. Her initial laboratory tests revealed a hematocrit of 0.36, a platelet count of 90×10^9 per liter (90,000 per μl), a prothrombin time of 14.2 seconds (control, 11.8 seconds), and a partial thromboplastin time of 79 seconds (control, 32 seconds). She received 2 additional units of fresh frozen plasma, but her prothrombin time and a partial thromboplastin time remained unchanged. She again received 2 units of fresh frozen plasma, and again her prothrombin time was 14.2 seconds (control, 11.8 seconds); this time the partial thromboplastin time was 32 seconds (control, 31 seconds). She required no further transfusion of blood or blood products. The endotracheal tube was removed on postoperative day 1, and she was discharged from the hospital on postoperative day 18.

The patient did well initially, but within a year the Luque rods had fractured, and in 1983 she underwent removal of the Luque rods under general anesthesia. Multiple pseudoarthroses were found between L-1 and L-5, but they were not repaired. No bone work was done, and blood loss was minimal. She again did well, but she had increasingly severe back pain and became wheelchair-dependent by 1989. She was observed for the next two years on multiple conservative treatments without success. In view of the continued severe pain, she was referred for anterior and posterior fusions of the spine from T-11 to S-1.

At a blood bank where the patient's blood was being collected for autologous transfusion, screening revealed that she was HIV-positive. Because she had no other risk factors, it was presumed that she had acquired HIV during her first operation. In view of her history of massive hemorrhage with her first back operation, and in view of her HIV-positive status, she was offered the use of aprotinin during the procedure on a compassionate-use basis. A protocol for the use of aprotinin was approved by the Stanford University Administrative Panel on Human Subjects in Medical Research, and the patient signed informed consent. Aprotinin (Trasylol) was provided by Miles Pharmaceutical Inc.

The patient was premedicated with midazolam hydrochloride after an intravenous line was placed. Anesthesia was induced with sodium thiopental after which pancuronium was given. Anesthesia was maintained with the use of isoflurane. A radial arterial line was then placed, and a central venous line was placed through the right internal jugular vein. A test dose of 500 kallikrein-inhibiting units (KIU) was given through the central line. There was no hemodynamic effect, and a loading dose of 2 million KIU was given over 30 minutes by the central line. The operation was begun with the patient in the left lateral decubitus position. Aprotinin was given continuously during the 11-hour procedure at a rate of 500,000 KIU per hour by the central venous catheter. The first portion of the operation was the anterior fusion from T-11 to S-1 carried out by thoracotomy, splitting the diaphragm, and using the tenth rib for a bone graft. There

was minimal bleeding during the retroperitoneal dissection and the disc removals, during which about 90% of each disc was removed. Following the anterior fusion, the diaphragm and pleura were closed and the patient was placed in the prone position where posterior fusions were done from T-11 to S-1. Bleeding was again minimal. During the entire procedure, the patient received 3 units of packed red blood cells and no blood products. She was taken to the intensive care unit, intubated, and placed on full mechanical ventilation. Her initial postoperative hematocrit was 0.34 (preoperative hematocrit, 0.32). The platelet count was 150×10^9 per liter (150,000 per μl), and the prothrombin and partial thromboplastin times were within normal limits. The endotracheal tube was removed on postoperative day 2 because of pain and splinting from her thoracotomy incision. Her postoperative course was complicated by small bowel ileus. She was discharged on postoperative day 11.

Nine months after the operation she is healthy, well, and much more comfortable. She has returned to work full time and is taking zidovudine prophylactically.

Discussion

Patients with HIV present a risk to surgical staff, especially if massive bleeding occurs during a surgical procedure. Patients who have had a surgical procedure in which massive bleeding has occurred are generally thought to be at risk for excessive bleeding during subsequent surgical procedures of a similar nature. Patients having major surgical correction of scoliosis are at a high risk of bleeding. This patient presented a difficult problem because she was thought to be at risk for bleeding during anterior and posterior spinal fusion from T-11 to S-1. She was also HIV-positive, and excessive bleeding during the long procedure would place the surgical staff at risk of exposure to HIV-positive blood. The patient was having severe pain, several attempts at medical management of her pain had failed, and she was now wheelchair bound and having difficulty carrying out her daily functions at work. The only option left for her was surgical therapy.

Aprotinin was used in an attempt to reduce blood loss during the procedure to minimize both the obvious risks to her as the result of bleeding and the risks to the surgical staff as they performed the operation. The operation during which aprotinin was administered was associated with minimal blood loss despite the fact that this procedure was more extensive than was the one in which massive bleeding occurred. The first bleeding episode may have been complicated by transfusion-related coagulopathy because both the prothrombin time and the partial thromboplastin time were prolonged, and the platelet count was mildly decreased. Nevertheless, heavy bleeding did not occur during the second procedure even though considerable dissection was carried out over a period of 11 hours. The major question that cannot be answered by this report is whether the use of aprotinin actually caused the minimal blood loss of the second operation. The surgeon reported a much drier field than he expected, especially considering the previous operation and the massive bleeding encountered then. That question can only be answered by a blinded, placebo-controlled trial of this type of operation.

Most studies that have evaluated the use of aprotinin in cardiopulmonary bypass have shown it to be effective in decreasing bleeding without increasing the risk of thrombotic complications.[1-9] There appear to be no adverse effects of aprotinin administration despite concerns about a procoagulant effect.[7] The use of aprotinin in noncardiac operations is not as well established, but there are several reports of its efficacy. Mallet and co-workers have described substantially less blood transfused in aprotinin-treated patients undergoing orthotopic liver transplantation.[12] In orthopedic surgery, Ketterl and associates showed a decrease in platelet aggregation during total hip replacement and a threefold reduction in transfusion requirement.[14,15] In neurosurgical procedures, aprotinin has been used to decrease the incidence of rebleeding in patients with subarachnoid hemorrhage.[16,17] The topical application of aprotinin has also been used to decrease intraoperative and postoperative bleeding in neurosurgical procedures.[18] The antifibrinolytic properties of aprotinin have been used to decrease bleeding in prostatic operations. One study combined the use of aprotinin with ε-aminocaproic acid and achieved a 50% reduction in blood loss in prostatectomy.[19]

The second question raised by this report is the mechanism of action whereby aprotinin decreased bleeding in this type of operation. Aprotinin use has been best studied in patients who are undergoing cardiopulmonary bypass wherein it is thought that exposure of the platelets to the bypass pump interferes with their function. The bleeding time is increased after cardiopulmonary bypass, and the use of aprotinin prevents this increase in bleeding time.[9] Aprotinin, a serine protease inhibitor, inhibits a large number of proteases. Serine protease inhibitors can be shown to inhibit a number of platelet functions. Various hypotheses have been used to explain how aprotinin may be improving platelet function and decreasing bleeding, but each has experimental evidence that casts some doubt on them.[7] In addition, aprotinin may be having an effect of inhibiting fibrinolysis. In liver transplantation, the major effect of aprotinin seems to be to decrease bleeding by inhibiting fibrinolysis.[10-12] This inhibition of fibrinolysis appears to be due to an inhibition of tissue plasminogen activator.[13] Although kallikrein inhibition, a known effect of aprotinin, may be responsible for this phenomenon, it has not been studied in liver transplantation.

Aprotinin may be improving platelet function and decreasing fibrinolysis in noncardiac operations by a similar mechanism to that seen during bypass procedures and liver transplantation. The degree of abnormality may not be as great as that seen in cardiac operations because the contact with the oxygenator may exaggerate the abnormalities in platelet function seen in those cases. Similarly, the effects on fibrinolysis may not be as great as the abnormalities seen in liver transplantation where the source of many coagulation factors is temporarily removed. The

beneficial effects of aprotinin use probably occur even before the carrying out of cardiopulmonary bypass, but its dramatic effect in these patients has meant that most investigators have focused their research efforts on that procedure. In noncardiac surgical procedures such as described in this report, trauma to scar tissue may release tissue plasminogen activator and activate fibrinolysis that, in turn, is attenuated by aprotinin. Unfortunately, no markers of hemostasis such as fibrin-degradation products were evaluated in this patient. Future controlled trials will offer the opportunity to evaluate the mechanism of action of aprotinin in noncardiac surgical procedures.

The case reported here may represent two possible uses of aprotinin that deserve further investigation: minimizing blood loss during an orthopedic operation and minimizing blood loss in HIV-positive patients requiring surgical therapy. The results also suggest that aprotinin may have beneficial effects in many surgical procedures not yet studied. The well-known dangers of bleeding during surgical procedures and of transfusion therapy make this an important subject worthy of further evaluation. The apparent safety of aprotinin administration means that the drug, if used in a wide variety of procedures, could have wide surgical application.

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Successful Enteral Refeeding After Massive Small Bowel Resection

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EXTENSIVE SMALL BOWEL RESECTION (>70%) is associated with severe nutritional consequences. The short-gut syndrome usually develops in patients with less than 150 cm of intact small bowel.[1] Malabsorption, dehydration, metabolic abnormalities, and nutrient deficiencies are possible problems if nutrition support is not implemented immediately after bowel resection.

Total parenteral nutrition (TPN), the most aggressive form of nutrition support, is usually necessary in the initial stages of recovery. The enteral route is preferred for long-term support, but tolerance is dependent on the extent of the small bowel resection, the site of remaining bowel (especially the ileum and ileocecal valve), the functional capacity of the remaining gut, and the presence or absence of concomitant gastrointestinal disease.[2] The amount of small bowel necessary for adequate nutrient delivery by the enteral route has been reported at variable lengths.

Report of a Case

The patient, a 62-year-old man, was admitted to the Level I Trauma Center at the University of New Mexico Medical Center (Albuquerque) with multiple stab wounds to his back and neck following a family altercation. Although enteral nutrition support (tube feeding) was started on the first day of hospital admission, TPN was instituted on day 5 because of tube feeding intolerance (diarrhea, abdominal distention). An exploratory laparotomy was done on hospital day 16 to rule out an intra-abdominal source for the patient's sepsis and abdominal distention, following which infarcted small bowel was resected from the proximal jejunum to the ileum. The distal ileum (57 cm in length), the ileocecal valve, and the colon were left intact.

After this operation, TPN was continued in amounts to meet the patient's estimated calorie and protein needs

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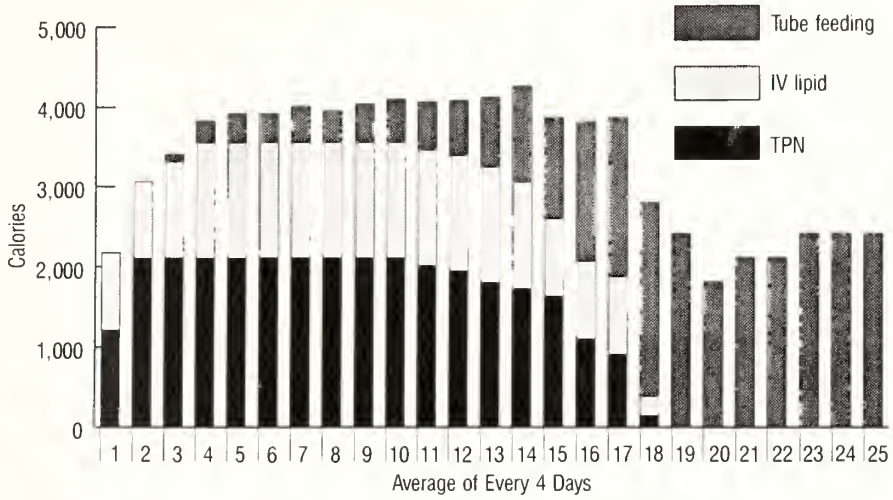

Figure 1.—The graph shows the patient's calorie intake by 3 different nutrition support delivery routes over an average of every 4 days after massive small bowel resection. IV = Intravenous, TPN = Total parenteral nutrition

until postoperative day 12 when the administration of the isotonic, peptide-based formula, Peptamen (Clintec Nutrition, Deerfield, Illinois), was started at 15 ml per hour through a small-bore feeding tube. This nutrition support regimen was continued for the next 20 days, at which time the tube feeding rate was increased by 5 ml per hour and then by 5 to 10 ml per hour on postoperative days 39, 46, 49, 52, 56, 60, 62, 63, 68, and 69. The parenteral nutrition and intravenous lipid rates were tapered accordingly until the tube feeding goal of administering Peptamen at 100 ml per hour was reached (Figure 1). Formed stools were noted after each tube feeding rate increase. The patient remained in positive nitrogen balance (+1, +2.2, +7, +4.7)* during the tube feeding rate progression (Figure 2). As more solid foods were tolerated, the tube feeding rate was also tapered accordingly.

When discharged on hospital day 112, the patient was consuming a low-fat, low-residue diet in six small feedings with oral formula supplements. Although serum albumin levels had decreased from 32 to 17 grams per liter (3.2 to 1.7 grams per dl) during the patient's septic episode, he was discharged with a serum albumin level of 30 grams per liter. His admission weight (59.2 kg) remained stable at the time of discharge (58.9 kg; see Figure 2).

The patient's follow-up visit two months after discharge showed that he was maintaining a good nutritional state. His weight (56.4 kg) was essentially stable. His visceral protein status had continued to improve, the serum albumin level being 40 grams per liter. Serum electrolyte, mineral, trace elements, and iron levels were all within normal limits.

*Nitrogen balances were calculated by subtracting 24-hour nitrogen losses (urine, insensible) from 24-hour nitrogen intake. The following equation was used:

[protein intake (grams/24hr)] ÷ 6.25 − [24-hr urine for urea nitrogen (grams) + 4 (insensible losses)]

A positive nitrogen balance indicates an anabolic state; a negative nitrogen balance indicates a catabolic state.

Discussion

After small bowel resection, intestinal adaptation occurs gradually, requiring more than a year to reach its maximum absorptive capacity. Hyperplasia of the microvilli, lengthening and dilation of the small bowel, and increased brush border enzyme activity all contribute to the increased surface area and absorptive capacity of the short gut.[3]

The delivery of enteral nutrients is the most important stimulus for mucosal growth and adaptation.[2] Numerous studies have been done to clarify the effects of different factors. Continuous enteral feedings of small volumes are more effective than intermittent doses of larger volumes. The flow of bile and pancreatic secretions stimulate mucosal growth distal to the point of delivery.[3] Secretin, cholecystokinin, glucagon, and enteroglucagon have all been suggested as trophic hormones for the gastrointestinal tract. Brush border enzyme activity increases according to the composition of the enteral feeding; more specifically, peptidases are stimulated by protein, disaccharidases by carbohydrate.[2]

Administering enteral feedings in the "elemental" form was originally favored for patients with impaired digestion and absorption.[4] The earliest elemental formulas contained protein as free amino acids, carbohydrate as glucose, and minimal quantities of fat. It was thought that providing nutrients in these forms facilitated maximal absorption. Clinical experience with these formulas has demonstrated frequent patient intolerance. The nausea, vomiting, and diarrhea that occurred were presumably due to formula hypertonicity—range, 500 to 910 mOsm per kg. Substantially diluted formulas were better tolerated, but their use resulted in inadequate nutritional intakes.

In comparison, accumulating information now suggests that peptide-based formulas have several advantages in patients with gastrointestinal compromise. Because different uptake carrier systems are used for amino

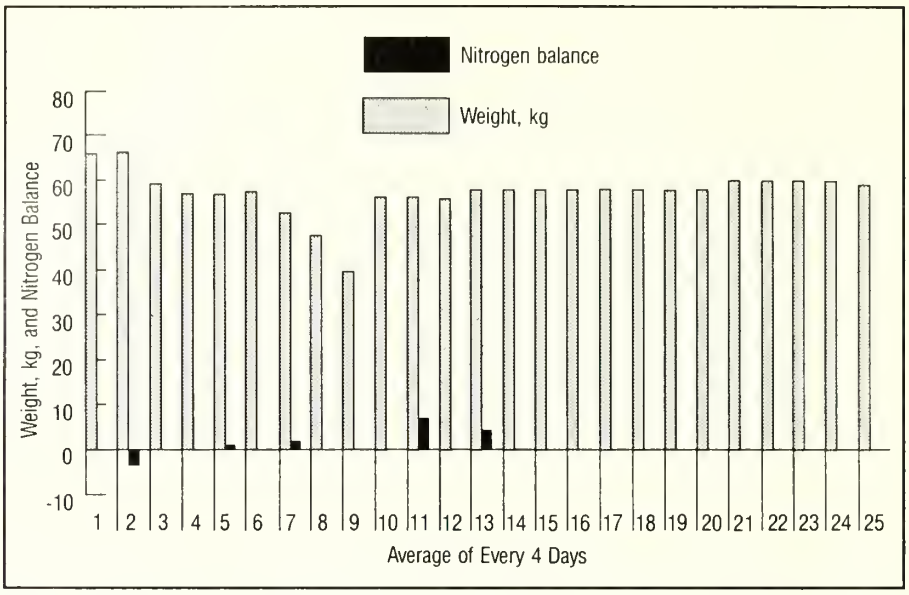

Figure 2.—The patient's nutritional status is demonstrated by nitrogen balance and weights over an average of every 4 days after small bowel resection.

acids and peptides, providing protein in both forms results in more rapid and efficient absorption.[4,5] Improved nitrogen use and retention and the maintenance of visceral protein status have been reported when the use of peptide-based formulas was compared with that of elemental diets.[5] A decreased incidence of diarrhea has also been noted with peptide-based formulas, due to presumably better absorption and low osmolalities. In addition, available data suggest that peptides stimulate a greater release of gut hormones and growth factors than do free amino acids, a particular advantage for patients with the short-gut syndrome.

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Topics in Primary Care Medicine

Early Diagnosis of Ectopic Pregnancy

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From 1970 to 1985, the number of ectopic pregnancies in the United States more than tripled, from 17,800 to 78,400, by the end of that period, representing 1 in every 66 pregnancies.[1] This increase is thought to be attributable to the rising incidence of salpingitis and improved methods of diagnosis and reporting. Although a sevenfold decrease in maternal mortality was observed during this same interval,[1] ectopic pregnancy continues to be the third leading cause of direct maternal death.[2]

Although the chief goal of treatment remains lifesaving intervention, early diagnosis and conservative management are aimed at preserving future fertility and reducing maternal morbidity.*

Risk Factors

Several risk factors are associated with ectopic pregnancy. Black women have a threefold increased risk of death from ectopic pregnancy compared with white women.[3] A history of salpingitis or pelvic inflammatory disease has been positively correlated with ectopic pregnancy.[4] A previous tubal operation, including sterilization, predisposes a woman to ectopic pregnancy. The incidence of ectopic pregnancy among all pregnancies after sterilization ranges from 15% to 20%.[5] The apparent increased incidence of ectopic pregnancy in women who use intrauterine devices is due to selection bias because those devices are more likely to reduce the number of intrauterine than of extrauterine gestations. Case-controlled studies have concluded that a woman who uses an intrauterine device has the same risk as a nonuser of an ectopic pregnancy.[6]

Women with a history of ectopic pregnancy have a 12% to 18% chance of recurrence in whatever tubes remain. Several studies have suggested that the relative risk of ectopic pregnancy is increased in women with infertility. It is unclear whether the risk is attributable to preexisting tubal disease, therapeutic manipulations to treat infertility, the use of ovulation-inducing agents or human gonadotropins, or advancing age. Additional reported causes of ectopic pregnancy include exposure to diethylstilbestrol in utero[7-9] and continued use of low-dose progestogen contraceptives. The risk associated with progesterone-only contraceptives may be due to their effect on tubal cilia in slowing ovum transport.[10]

Inquiring about related history is vital in assessing a symptomatic woman's risk for ectopic pregnancy. In a recent study of 161 patients presenting to an emergency department with a proven ectopic pregnancy, however, 43% of the women denied any known risk factors, even on follow-up questioning.[11] Thus, a high suspicion for the diagnosis is advisable even in the absence of identified risk factors.

Clinical Presentation

The clinical presentation of ectopic pregnancy varies from nonspecific abdominal symptoms to overt hemodynamic instability. Abdominal pain, a history of amenorrhea, and irregular vaginal bleeding are the most common symptoms of an ectopic pregnancy, but this classic triad is seen in less than 50% of early patients presenting with confirmed ectopic pregnancy[12] and is not specific for the diagnosis.

Abdominal pain is almost always present before rupture, but the time of onset, severity, location, and character of the pain are unpredictable. Abdominal pain caused by tubal distension usually commences three to five weeks after the missed menses. Half to three quarters of women with ectopic pregnancy report some period of amenorrhea.[13] In the absence of amenorrhea, the diagnosis of pregnancy is less apparent. Irregular scanty vaginal bleeding may be misinterpreted as menstruation. Other symptoms may include nausea, vomiting, tenesmus, and lightheadedness or syncope.

On physical examination, an unruptured ectopic pregnancy is usually reflected by localized lower quadrant tenderness. Once tubal rupture or retrograde bleeding from the implantation site occurs, the resulting hemoperitoneum produces peritoneal irritation manifesting as guarding and rebound tenderness. A palpable adnexal mass is noted in only half the patients with ectopic pregnancies.[14] Thus, the absence of an adnexal mass does not exclude the diagnosis.

Other findings may include cervical motion tenderness and adnexal tenderness. The uterus is usually normal in size but may be enlarged from deciduation or accumulated blood. Most patients are afebrile. Orthostatic blood

*See also the editorial by E. D. Schriock, MD, "Ectopic Pregnancy—Becoming a Nonsurgical Disorder," on pages 210-211 of this issue.

(Lawlor HK, Rubin BJ: Early diagnosis of ectopic pregnancy. West J Med 1993; 159:195-199)

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TABLE 1.—*Clinical Presentation in Confirmed Ectopic Pregnancy*

Study	Patients, No.	Abdominal Pain, %	Rebound, %	Vaginal Bleeding, %	Amenorrhea, %	Adnexal Mass, %	Nausea, Vomiting, %	Dizziness or Syncope, %
Breen, 1970[14]	654	100	52	80	84	49	17	17
Helvacioglu et al, 1979[13]	284	97	41.2	55	74	29.9	31	31
Sandvei, 1981[15]	450	83.8	--	83.8	--	74.7	18.7	23.1
Stovall et al, 1990[11]	161	56.6	--	58.3	62.1	21.1	--	--

pressure and pulse changes will identify those patients with hypovolemia due to hemoperitoneum. Table 1 summarizes presenting signs and symptoms associated with ectopic pregnancies.[11,13-15]

The early stages of an ectopic pregnancy may mimic other abdominal or gynecologic conditions. Ectopic pregnancies are frequently misdiagnosed as an incomplete or threatened abortion, intrauterine pregnancy, a ruptured corpus luteal cyst, dysfunctional uterine bleeding, or pelvic inflammatory disease. In a recent review of the records of pregnant women presenting to an emergency department where 1 of every 13.4 confirmed pregnancies was ectopic, 45% of those women ultimately confirmed as having an ectopic pregnancy were discharged home after their first emergency department visit with a diagnosis of threatened abortion, intrauterine pregnancy, cystitis, or other incorrect impressions.[11]

The nonspecificity of clinical signs and symptoms associated with ectopic pregnancies emphasizes the need for clinicians to have a high index of suspicion in considering this disorder. It also underscores the difficulty of making the diagnosis on clinical grounds alone. A correct diagnosis of unruptured ectopic pregnancy is made in less than 50% of confirmed cases.[11]

Diagnostic Tests and Their Limitations

Human Chorionic Gonadotropin Assay

The primary biochemical diagnostic test used in the differential diagnosis of symptomatic women of reproductive age is the human chorionic gonadotropin (hCG) assay. Assays with sensitivities of 15 to 50 IU per liter (15 to 50 mIU per ml) will detect pregnancy (intrauterine as well as ectopic) at the time of expected menses or approximately seven days after implantation. False-negative results are extremely rare (less than 1%) at this level of sensitivity but do occur.[16] Because the risk of a false-negative result depends on the cutoff level, clinicians should know the level of sensitivity if qualitative testing is used. When quantitative hCG assay results are available promptly, they should be used rather than qualitative testing of blood or urine.

Ectopic pregnancies generally produce a lower level of hCG than normal pregnancies.[17] Individual variations in levels of hCG are large enough, however, that normal and pathologic levels overlap substantially at a given gestational age. Therefore, a single quantitative hCG assay is of limited value in distinguishing ectopic pregnancy from normal pregnancy. The rate of hCG production in early pregnancy is a useful discriminator between normal and abnormal pregnancies. Kadar and colleagues have calculated that the doubling rate of serum hCG in intrauterine pregnancies is 1.4 to 2.1 days.[18] In contrast, abnormal pregnancies (including ectopic pregnancies) produce less than a 66% increase in hCG levels over the same interval. Serial hCG assays performed at 48-hour intervals allow pain-free, clinically stable women who are at risk for an ectopic pregnancy by history and symptoms and who have a positive hCG assay result but nondiagnostic ultrasound findings to be diagnosed noninvasively while being observed closely by their clinician.

Transabdominal Pelvic Ultrasonography

The primary value of ultrasonography is to rule out an ectopic pregnancy by identifying an intrauterine pregnancy.[19-21] The reliability of ultrasound studies depends on the gestational age of the fetus (embryo).

The earliest evidence on transabdominal pelvic ultrasonography of an intrauterine pregnancy is visible at about 6 weeks' gestational age. Findings that indicate an intrauterine pregnancy at this stage of development are the presence of an intrauterine gestational sac or a "double-density" gestational sac. At 7 to 8 weeks' gestational age, an embryo becomes visible. Gestational age is often difficult to determine, however, because many women do not remember the date of their last menstrual period; this makes the reliability of ultrasound findings difficult to assess. At hCG levels of 6,000 to 6,500 IU per liter, intrauterine pregnancies can be detected by ultrasonogram 94% of the time.[22,23] These levels correlate with roughly 5 to 6 weeks' gestational age. Thus, the absence of ultrasonographic evidence of an intrauterine pregnancy in a symptomatic woman with hCG levels greater than 6,000 IU per liter should be considered an indication of an ectopic pregnancy until proved otherwise. The positive predictive value of such a finding is 95%.[24] This level of confidence requires an experienced ultrasonographer and high-resolution ultrasound equipment. The only specific evidence of an ectopic pregnancy on transabdominal ultrasonography is fetal heart activity in the adnexa. This is an uncommon and late finding.

At hCG levels of less than 6,000 IU per liter, other ultrasonographic findings suggestive of an ectopic pregnancy are noncystic, complex adnexal masses and free fluid in the pelvic peritoneum. Although this is nonspecific evidence, in a patient with a positive hCG assay result it carries a positive predictive value of 83% to 94%.[19,25] The absence of such findings does not rule out an ectopic pregnancy, however. Because more than 60% of women suspected of having ectopic pregnancies present with hCG levels of less than 6,000 IU per liter,[22]

transabdominal ultrasonography has limited usefulness in this population.

There are rare occurrences of combined intrauterine and extrauterine pregnancies. This finding has increased in frequency since the introduction of ovulation-inducing agents and is now reported to occur in 1 of 3,500 to 1 of 15,000 pregnancies.[26] Therefore, a history of infertility procedures should alert a clinician to this unusual possibility when reviewing ultrasound results.

Transvaginal Pelvic Ultrasonography

Transvaginal pelvic ultrasonography has permitted finer resolution and visualization of uterine and adnexal findings at earlier gestational ages than transabdominal techniques, thus aiding in the diagnosis of an ectopic pregnancy when hCG levels are less than 6,000 IU per liter. In studies of patients with normal intrauterine pregnancies and those in whom a diagnosis of ectopic pregnancy was being considered, transvaginal ultrasound studies were consistently able to identify intrauterine gestational sacs at hCG levels of 1,000 to 2,000 IU per liter or at about 32 days' gestational age.[27,28] As such, transvaginal ultrasonography is able to confirm findings of intrauterine gestation at least a week earlier than transabdominal ultrasonography and at much lower hCG levels. Thus, the absence of transvaginal ultrasonographic evidence of an intrauterine pregnancy in a symptomatic patient with hCG levels greater than 1,000 IU per liter should be considered an indication of an ectopic pregnancy until proved otherwise.

Transvaginal ultrasonography is also superior to conventional transabdominal ultrasound studies in identifying adnexal and peritoneal abnormalities. In a study of 34 patients, 25 of whom had surgically confirmed ectopic pregnancies, characteristic adnexal masses consistent with an ectopic pregnancy were noted in 84% of patients studied transvaginally but in only 68% of those who had transabdominal ultrasonography. Adnexal gestational sacs were seen in 64% of patients with transvaginal ultrasonograms but in only 32% of those with transabdominal ultrasonograms.[29] The improved sensitivity of the transvaginal technique has been confirmed by other researchers.[30] Because transvaginal ultrasonography is also sensitive and specific in detecting even small amounts of blood (75 to 100 ml) in the cul-de-sac before rupture has occurred,[28] it may replace culdocentesis as a noninvasive test for the diagnosis of an unruptured ectopic pregnancy.

Although a late finding, fetal cardiac activity in the adnexa is more easily detected on transvaginal ultrasound.[31] This technique also yields more reliable data in obese women being evaluated for ectopic pregnancy.

The greatest clinical assistance offered by this technique is the ability to diagnose ectopic pregnancies at an earlier gestational age and before rupture occurs. In the series reviewed here, 86% and 88% of all patients with ectopic pregnancies were diagnosed with unruptured ectopic pregnancies amenable to conservative surgical therapy.[28,29] Early diagnosis of ectopic pregnancy enables the clinician to achieve tubal salvage more frequently and allows the patient to escape the added morbidity of major intra-abdominal bleeding and surgical treatment.

Culdocentesis

The limitation of culdocentesis is that it can identify a hemoperitoneum but not its source. Thus, a ruptured luteum may mimic an ectopic pregnancy and yield abnormal findings on culdocentesis. In a patient with an unruptured ectopic pregnancy or when the blood loss is small, the findings of culdocentesis may be falsely negative or nondiagnostic.[9]

The combination of an abnormal culdocentesis result and a positive hCG assay is predictive of 99% of ruptured ectopic pregnancies.[32] Many clinicians think that the therapeutic value of this painful procedure is low because transvaginal ultrasonography is a sensitive marker for the presence of free pelvic peritoneal blood. Culdocentesis can be helpful in determining the need for immediate surgical intervention in patients with ruptured ectopic pregnancies.

Progesterone Assay

Since 1978 it has been noted that progesterone synthesis by the corpus luteum is decreased in abnormal gestations compared with that occurring in a viable intrauterine pregnancy.[33] This impaired corpus luteal function is independent of decreased hCG levels; unlike hCG levels, serum progesterone levels are not gestational-age dependent.[34]

Ectopic pregnancies, incomplete and complete abortions, blighted ova, and first trimester intrauterine death are all associated with decreased progesterone levels.[33] Several studies have examined the prognostic value of the serum progesterone level in predicting ectopic pregnancies. In two studies, 96% and 97% of confirmed early ectopic pregnancies were associated with progesterone levels of 79.5 nmol per liter (25 ng per ml) or less.[11,35] At progesterone levels of greater than 79.5 nmol per liter, the likelihood of an ectopic gestation is very low.

While sensitive for detecting an ectopic pregnancy, progesterone screening is not particularly specific. In one study, 24% of patients with normal intrauterine pregnancies had low progesterone values.[11] No cases have been reported of normal pregnancies with progesterone values of less than 15.9 nmol per liter (5 ng per ml). Therefore, pregnant patients with progesterone levels this low have a 100% likelihood of an abnormal pregnancy. The value of this test will depend on the likelihood of an ectopic pregnancy in a particular patient, reflected by her risk factors and clinical presentation. When the results of a progesterone assay can be obtained within 24 hours, this assay may be part of an approach in evaluating clinically stable women at risk for early ectopic pregnancy.

Conclusion

Ectopic pregnancy in a clinically unstable patient is usually evident. Blood and fluid therapy should be instituted promptly and an exploratory laparotomy performed. Diagnostic problems arise when a pregnant woman who

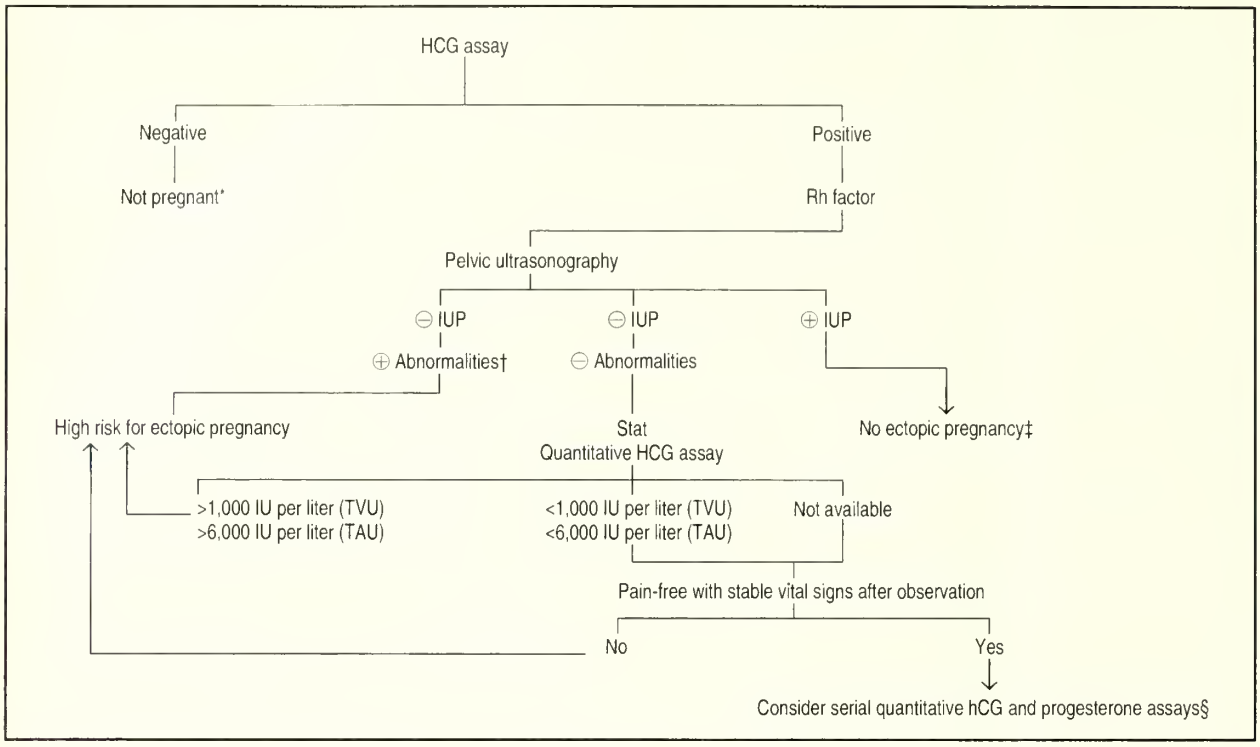

Figure 1.—The algorithm describes the diagnostic decision points used to evaluate women presenting with a history or symptoms suggestive of a nonruptured ectopic pregnancy. *This study has a 1% false-negative rate. †These include noncystic adnexal masses, free peritoneal fluid, and an adnexal gestational sac. ‡The rare possibility of an intrauterine and ectopic pregnancy coexisting should be considered. §See text for description. hCG = human chorionic gonadotropin, IUP = intrauterine pregnancy, TAU = transabdominal ultrasonography, TVU = transvaginal ultrasonography

is clinically stable presents with symptoms that are consistent with an ectopic pregnancy.

The algorithm shown in Figure 1 is a suggested evaluation protocol based on the availability of diagnostic tests. When a clinically stable woman has nondiagnostic findings on ultrasound studies or culdocentesis, obstetric-gynecologic consultation is strongly suggested, not only because these are often equivocal presentations (with a major risk of morbidity or death in the event of an incorrect diagnosis), but also because the consulting physician should be involved in the ongoing evaluation of the patient (serial hCG assays, ultrasound evaluations, and the like).

Any patient in whom the diagnosis of ectopic pregnancy has not been ruled out should receive clear and specific instructions from the treating clinician on the diagnosis being considered, the risks involved, and symptoms that warrant a prompt return for further evaluation, as well as specific instructions for follow-up evaluation no later than the next day.

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This article is one of a series on topics in primary care in which common diagnostic or therapeutic problems encountered in primary care practice are presented. Physicians interested in contributing to the series are encouraged to contact the series' editors.

STEPHEN J. McPHEE, MD
TERRIE MENDELSON, MD
Assistant Editors

* * *

COVERT SYMPTOMS

When the cement stair divides, I cannot
find the riser, cannot place my foot
within the space between step and air.
I wait for someone to take my hand,
for the shapes to hold
so I can go up or down.

In the doctor's office, the examining table
separates into two, one catercornered
and slightly above the other.
They do a slow join until one overlaps.
On the narrow, white pallet, my head
helmeted like an astronaut's,
while the technician reads my brain, I lie still.
The sound is a rain of bullets.

So: the disease is physical,
misfiring synapses:
I can make do with this,
I had thought I was crazy. Back home
I mix dough to a sponge and let it rise,
add salt and oil and flour, pound
the risen bread down and beat on it
with the heels of my hands.
Between the risings, two suns
come together through the trees.

SUSAN RONEY-O'BRIEN
Princeton, Massachusetts

Commentary

Academe and Government
Firm Link or Broken Reed?

ROBERT G. PETERSDORF, MD, *and* KATHLEEN TURNER, MPA, *Washington, DC*

The federal government has been such an important partner in many academic medical center activities that we take both its presence and the support it provides to our institutions for granted.* We tend to comment on the relationship only when we think it is going awry because of changes in federal policy or funding. We seldom question whether those in the federal government think the relationship has faltered through some action or inaction of our own. The link between the federal government and academic medical centers is unique and pervasive. That involvement relates to the following activities of the academic medical center:

- The research activities of medical faculty have been primarily supported by the National Institutes of Health (NIH), based on a policy decision that it would be in the government's best interest to support a broad array of research projects primarily through universities rather than through independent research institutes or intramural laboratories.
- The teaching activities of the academic medical center have been supported less directly, but supported nonetheless, through programs such as the now defunct capitation initiative, through project grants for special curricular innovations, and through the student assistance programs that finance medical student education.
- Federal involvement in patient care activities evolved through the passage of Medicaid and Medicare legislation in the mid-1960s, assuring medical centers of a payment source for elderly and indigent patients who are disproportionately treated at academic medical centers and their affiliated hospitals.
- The affiliations that exist between medical schools and the hospitals of the Department of Veterans Affairs crosscut all activities of academic medical centers and contribute to their research, patient care, and teaching missions.

The level of federal support for the activities of academic medical centers during the past three decades has been substantial, although a notable decline has occurred in the proportion of overall support that comes from federal dollars. Nevertheless, the federal contribution to medical school activities in fiscal year 1991 amounted to more than $4.6 billion (Figure 1). During this same 30-year period we also saw an enormous increase in the proportion of medical school revenues from medical service income, which rose from $28 million to $9.4 billion (Figure 2). Of personal health care expenditures, 30% are borne by Medicare and Medicaid, which play a substantial federal role in generating medical school income.

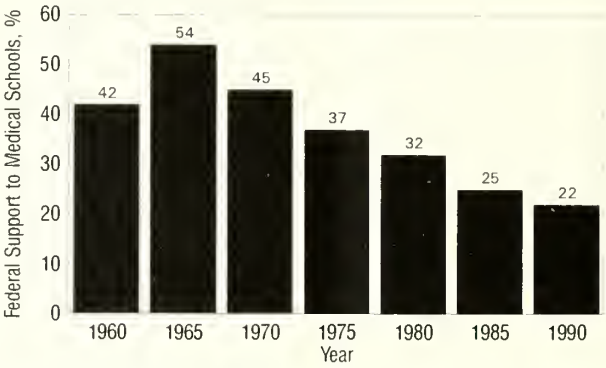

Figure 1.—The proportion of medical school revenues from the federal government, excluding services, has fallen from 54% in 1965 to 22% in 1990.

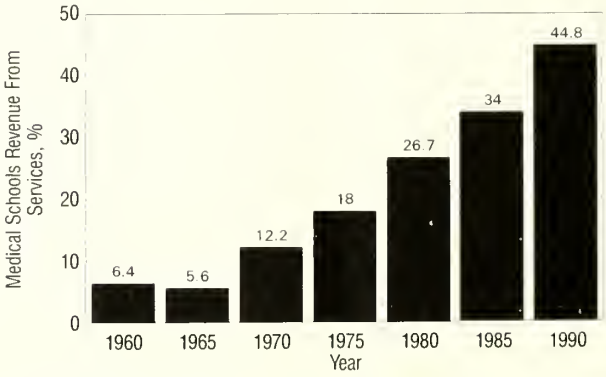

Figure 2.—Medical services as a source of medical school revenues have risen steadily since 1965.

*See also the editorial by Lloyd H. Smith, Jr, MD, "Government and the Academic Health Science Center" on pages 211-212 of this issue.

(Petersdorf RG, Turner K: Academe and government—Firm link or broken reed? West J Med 1993; 159:200-207)

From the Association of American Medical Colleges, Washington, DC.

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ABBREVIATIONS USED IN TEXT

GME = graduate medical education
IME = indirect medical education [adjustment]
NIH = National Institutes of Health
PPS = prospective payment system
VA = Veterans Administration [Department of Veterans Affairs]

It seems especially appropriate in these early months of the Clinton Administration to be discussing the link between the federal government and our academic medical centers. After 12 years of a Republican administration, we can surely expect to see President Clinton proposing changes. The most fundamental change affecting our institutions will likely be in the realm of health care reform and related efforts to control costs.

Research

For most of the 1960s and 1970s the federal government accounted for about 60% of the national annual investment in biomedical research; industry accounted for 25% to 30%. This situation is the consequence of a major federal investment in biomedical research that began with World War II. Contributions by private industry to research funding accelerated in the 1980s, spurred by advances in biotechnology, pharmaceuticals, and medical instrumentation. By 1990, of the $23 billion in total research and development expenditures, about 46% was funded by private industry, 42% by the federal government, and 12% from other sources, including states and private, nonprofit foundations and agencies.

In the medical school setting, however, despite the initiation of academic partnerships with industry, the main sponsors of faculty research have been federal agencies. In 1991, medical schools reported receiving sponsored research funding of $3.4 billion, of which three fourths was provided by the federal government, most of that from the NIH. As a result, the funding patterns, the leadership, and the major policy directions of NIH are a focus of intense interest to the academic community.

In the 1950s and 1960s, annual growth in NIH appropriations was brisk—more than 20% after inflation. In the 1970s, growth in support continued but was more modest—approximately 5% annually. In the 1980s the size of funding increases diminished considerably, giving rise to conflicts within the biomedical community about the appropriate allocation of funds within programmatic divisions and within funding mechanisms (Figure 3).

National Institutes of Health Strategic Plan

The plateau in funding led to an important unfinished chapter from the last administration, the NIH Strategic Plan.[1] Then-Director Bernadine Healy thought that the plan would be the instrument to revive lagging biomedical research funding.

When last reviewed, the plan was 400 pages long. Despite its length, the plan's design was comparatively simple, consisting of a mission statement, four specific goals,

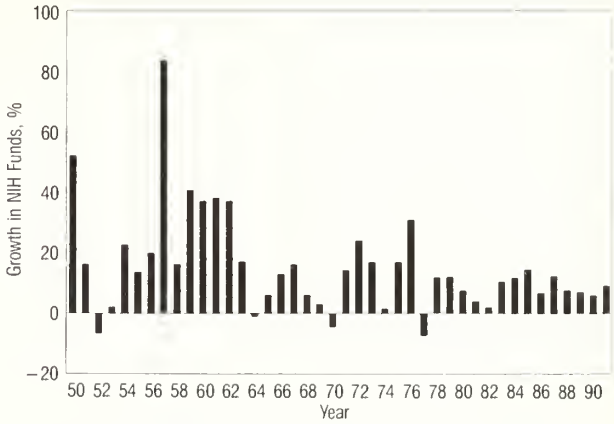

Figure 3.—The yearly growth in total congressional appropriations to the National Institutes of Health (NIH) stabilized in the 1980s (personal communication from the Division of Financial Management, NIH).

six trans-NIH objectives, and an implementation strategy. The meat of the plan is contained in the six trans-NIH objectives:

- *The advancement of critical science and technology.* Under this rubric are contained molecular medicine, biotechnology, molecular immunology and vaccine development, structural biology, and cellular and integrative biology.
- *Progress on critical health needs.* This objective covers biology and the environment, child health, chronic illness, and the health of minorities and underserved populations.
- *Increased investment in intellectual capital.* The third objective deals with development of the talent base, the importance of public understanding of science, and professional standards for scientific research. The issue here is whether the human and fiscal capital will be available to implement these objectives.
- *Improvement and expansion of research capacity.* This plank deals with research facilities, instrumentation, and computational research and touches on the role of the NIH intramural programs. The bottom line: more money.
- *Improved stewardship of public resources.* Under this objective are lumped the mechanisms of extramural funding, such as R01s (individual investigator-initiated grants to support discrete, circumscribed projects) versus program projects or centers; ways in which priorities are set; and the complex issues of peer review. The peer review process may be due for some overhaul.
- *Solidification of public trust.* This objective deals with improving NIH's public image, an objective with which few could argue.

The reaction of the extramural community to the plan, though initially somewhat rancorous, settled some time ago into a state of cool civility.[2] Despite all the effort to solicit external advice, there seems to be skepticism concerning the planning effort and its effect on extramural research programs. Some question the need for the plan at all, given the existing planning efforts of individual institutes. Some are uncomfortable with the emphasis of the

plan on national economic returns as a justification for research. The concern is that, based on the plan, NIH will derive its priorities with too heavy an emphasis on political and economic considerations and insufficient regard for investigator-initiated ideas and scientific opportunity. Related to this concern is the fear that an investigator whose work does not fall within a "critical technology" will be at a disadvantage.

The plan's future is somewhat uncertain. The final document is in the process of being edited and pared down to about 100 pages. The receptivity of the Clinton Administration to the plan is unknown, but it is hard to imagine, given the substantial resources required to produce it, that the plan could be rejected out of hand.

Justifying Research on Economic and Social Grounds

One topic receiving progressively more attention is the extent to which public support of research should be justified on grounds other than the intrinsically noble pursuit of scientific truth. For many, science for science's sake is no longer sufficient justification. Congress and, presumably, the public are increasingly looking to research for economic returns and direct applications and benefits for public health.

An emphasis on economic and societal returns is cropping up not only in the strategic plan but in other venues. Representative George Brown (Democrat, California), Chair of the House Committee on Science, Space, and Technology, thinks there is a worrisome gap between the knowledge that our scientific enterprise is yielding and the needs of our society. A report to his committee by a specially convened task force called for developing mechanisms to link research to the long-term national goals of "economic competitiveness, human health, and environmental protection."[3] Brown himself emphasized this view when he wrote,

> Society needs to negotiate a new contract with the scientific community. The contract must be rooted in the pursuit of explicit, long-term social goals. . . . A new contract will measure the value of research and innovation not by number of publications or citations or patents, but by progress toward these specific goals ("It's Down to the Last Blank Check," *Los Angeles Times*, September 8, 1992, p 5).

The Carnegie Commission on Science, Technology, and Government recently released a report that identifies "a reliable, sustainable, and competitive economy" as one of four major classes of societal objectives to be met by our scientific endeavors.[4]

The emphasis on social and economic returns from the public investment in research has been beneficial for academic institutions. This emphasis has led to policies that have allowed them to profit financially from innovations derived with federal support. At the same time, the effect of these policies on the academic culture and on the NIH has been called into question. The fear, of course, is that unfettered exploration of new scientific opportunities will become a thing of the past, supplanted by a single-minded drive toward all things profitable; that NIH's tradition of supporting the research ideas that flow freely from the wellspring of our investigators' creative minds will be overtaken by an overly constrained, economically driven research agenda. Economic competitiveness should be a natural derivative of a vigorous national biomedical research enterprise, but not a primary goal. We must recognize the important benefits stemming from the growing collaborations between industry and academia, but underscore NIH's vital role in supporting the academic values of our institutions and in assuring healthy and vigorous national programs in support of fundamental research.

The New Administration

How the transition from a Republican to a Democratic administration will affect biomedical research is not entirely clear, though based on comments Clinton made during his campaign, it is likely that there will be continued emphasis on the link between basic research and economic success. In an interview published in *Science*, Clinton said[5]:

> The linkages between basic research and technology are becoming increasingly prevalent. The absence of a clear technology policy is one of the key reasons why America is trailing some of its major competitors in translating its strength in basic research into *commercial success* [emphasis added].

The persons who Clinton appoints to key positions within the administration will influence many aspects of the research agenda, and it may be some time before we see how that agenda is evolving.

Education

Federal government support for medical education has been confined to specific, targeted initiatives, generally related to workforce policy. The most comprehensive example of these programs occurred 30 years ago when Congress enacted the Health Professions Educational Assistance Act.[6] The major impetus for passage of the act was the public perception that the number of physicians in the United States was inadequate. The legislation sought to alleviate this problem by providing funds for the construction of teaching facilities, for loans, and later, for scholarships for students in the health professions.

Amendments to the legislation expanded the scope of government assistance to medical education by providing funds for educational improvements and other special projects and eventually for capitation grants based on class size. Participation in the program was tied to a commitment by the schools to expand class size to address the perceived physician shortage that was the original impetus for the legislation.

Despite the opposition of organized medicine, academic medicine welcomed this federal largesse and responded enthusiastically, increasing the number of medical schools by 50%—from 83 at the time the legislation was passed to 126 today. The number of medical students doubled in this same period from just over 31,000 to a peak enrollment of more than 67,000 in 1984 (Figure 4).

As early as 1970 Congress considered that it was essential not only to promote the production of physicians

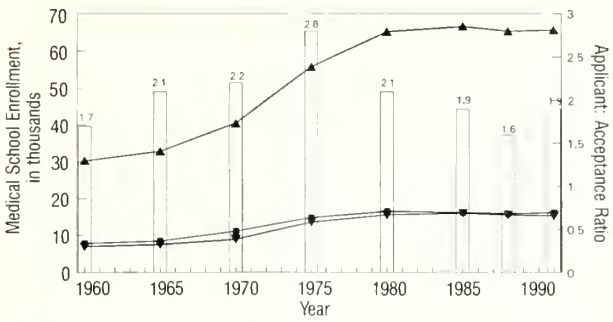

Figure 4.—During the 1980s medical school enrollment stayed steady (▲ = total enrollment, ■ = first-year new entrants, ▼ = graduates) despite a sharp decline in medical school applicants (vertical bars) since a historical high in 1975 (from the AAMC Data Book, Association of American Medical Colleges, Washington, DC, 1992).

generally but particularly to increase the number of primary care physicians. Just a decade after the passage of the original authorizing legislation, public policymakers had discovered a hard truth—that merely increasing the number of physicians apparently was not going to solve the country's health problems and physician distribution inequities. Federal policy shifted, and general assistance to medical education was eliminated in favor of support for more targeted programs. As Senator Richard Schweiker said of this legislative shift[7]:

> So long as the medical education system is going to accept and demand 55% federal support, we in the federal government have a right to ask that doctors be in the right place and trained in the right specialty.

This view was echoed two years later when the Secretary of Health, Education and Welfare at the time, Joseph Califano, addressed the 1978 annual meeting of the Association of American Medical Colleges. The gist of his talk included a charge that medical schools were not training a sufficient number of primary care physicians and that the physician community must become more responsive to demographic, social, and economic forces. He called the decline in the proportion of primary care physicians "disturbing" and said,[8]

> Already we can see some unhappy results of this sharp decline in primary care physicians. Large numbers of patients are resorting to hospital emergency rooms for care because they do not have access to a family physician. The health care market place is becoming increasingly confused as patients act as their own medical managers, referring themselves to highly sophisticated specialists for relatively routine complaints. This is not only inappropriate but expensive. The entire health care delivery system is unnecessarily skewed toward the most expensive specialty end of the spectrum.

Califano was absolutely on target in this assessment, and his remarks remain as true today as they were 15 years ago. It is noteworthy that as long as 15 years ago important policymakers in both the executive and legislative branches were "fed up" with the inability of the medical education system to respond to a national need for more primary care physicians. The medical profession should consider itself lucky that there has not been a specific legislative initiative that would mandate changes in medical student and resident education to accomplish the goal of more primary care physicians. Perhaps this respite can be credited to the change in the philosophy of what government should do, as opposed to what it can do, that was the hallmark of the "Reagan Revolution," but it is clear that both the philosophy and the policies of that revolution are in the process of being reversed.

Today, there are only a few categorical grant programs that are the legacy of the original federal incursion into medical education (Table 1). In fiscal year 1993 they will provide $90 million to support various primary care efforts, including attempts to promote medical education in rural areas through the area health education centers.

A less direct federal method of supporting medical education has been the student assistance programs (Figure 5). In the academic year 1990-1991, $826.5 million in loans and scholarships was made available to medical students, of which more than three fourths relied on federal support.

TABLE 1.—*Federal Government Support of Medical Education, Fiscal Year 1993*

Federal Program	*Appropriation, in million $*
Area health education centers	19.8
Family medicine departments	5.5
General internal medicine and pediatrics	16.9
Family medicine residencies	32.7
Preventive medicine residencies	1.6
Geriatric training and research	13.6

A disturbing phenomenon occurred in the previous Congress with the reauthorization of some of these programs. The reauthorizing legislation deliberately incorporated primary care requirements into three student financial aid programs that had previously been strictly needs-based. Notice has been served that additional student aid programs facing reauthorization in 1993 may include similar restrictions. Serious questions have been raised about the equity of creating these dual objectives and requirements. These new requirements to render medical service in primary care can be interpreted as im-

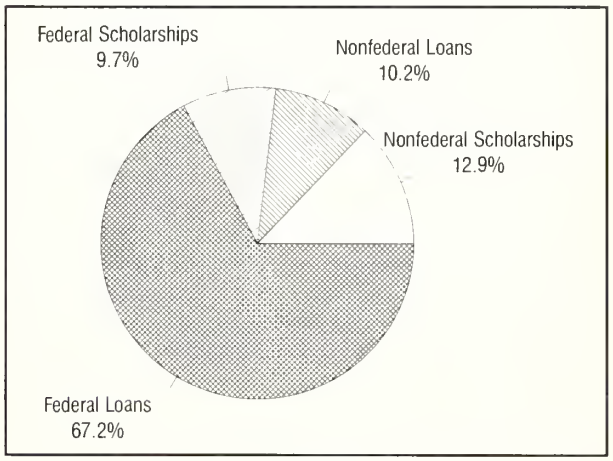

Figure 5.—Federal loan programs are the major source of medical student financial assistance.

posing a disproportionate responsibility for fulfilling community-oriented personnel needs on needy students.

Besides the more restrictive provisions for students seeking such financial assistance, these health professions student loan programs impose stiff penalties on the sponsoring schools that have too few graduates selecting primary care as a career option. These schools will be required to return to the government a portion of the federally contributed capital in the institution's revolving loan fund, decreasing funds available for students in future years.

A message is being sent to our community that we have failed to meet the perceived national need for generalist physicians and that coercive methods will be used if we continue to fail to respond to this need voluntarily.

Patient Care

The institution of Medicare and Medicaid in 1965 had several profound effects on academic medical centers:

- Medicare and, to a lesser extent, Medicaid provided financial stability for academic medical centers by identifying a payment source for patients who had previously been given charity care. This was especially important for medical schools located in inner cities and in other areas with large medically indigent populations.
- From the beginning, the Medicare legislation explicitly included the cost of graduate medical education (GME) as a legitimate component of reimbursement for patient care. This not only stabilized GME programs and their financing, but probably contributed to the growth of residencies and fellowships.
- With faculty members able to secure reimbursement for more of their patient care, the practice plan became a viable source of income to support other medical center activities.
- Clinical work became as central to the academic enterprise as did teaching and research; to respond to the clinical mandate, new systems of faculty appointment, evaluation, and advancement were established. An exponential growth in the number of clinical faculty occurred; the number of full-time faculty in clinical departments increased from 11,447 in 1965 to 64,115 in 1991.
- The structure of the Medicare reimbursement system favored specialty care. Responding to these incentives, the teaching hospital became a bastion of tertiary care and subspecialty education.

Hospital Payment

The 1980s will be remembered as the decade in which a prospective payment system (PPS) for Medicare based on diagnosis-related groups replaced cost-based reimbursement. We are now in the tenth year of this system, and, by most accounts, it has been a success primarily because it has constrained costs (Figure 6).

When the prospective payment system was implemented, it was feared that teaching hospitals would fare the worst. Reality has not borne out these fears (Figure 7). As a group, teaching hospitals continue to have higher

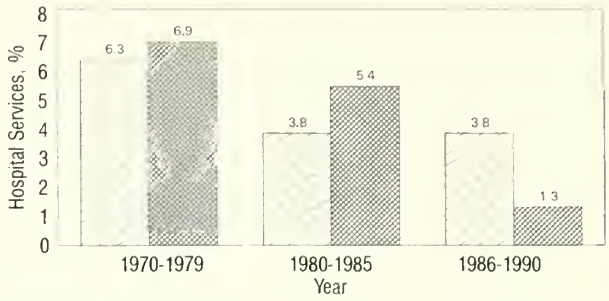

Figure 6.—Changes in real national and Medicare hospital expenditures, per capita and per enrollee, are shown. With the advent of the prospective payment system, Medicare expenditures (▩) for hospitals increased less rapidly than the national average (▨) (from Medicare and the Prospective Payment Assessment Commission).[9(p17)]

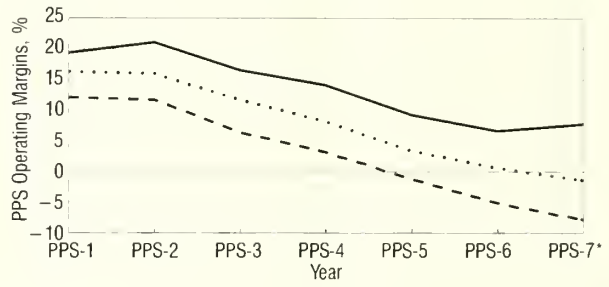

Figure 7.—Operating margins for teaching hospitals in the first 7 years of Medicare's prospective payment system (PPS) are greater for major and other teaching hospitals (solid line, dotted line) than for nonteaching hospitals (dashed line) (from Medicare and the Prospective Payment Assessment Commission).[9(p52)] * = preliminary data

operating margins under the system than do nonteaching hospitals because teaching hospitals receive a special payment adjustment, the indirect medical education adjustment (IME), for their higher costs associated with severity of illness and the presence of graduate physician trainees. Many, but by no means all, teaching hospitals also receive the disproportionate share adjustment, a mechanism for transferring additional federal funds to hospitals that serve a large share of Medicaid and other low-income patients. Hospitals that get both these adjustments in payments have the highest PPS margins of any group at 3.8%. Hospitals that get only IME payments have negative PPS margins (Figure 8).

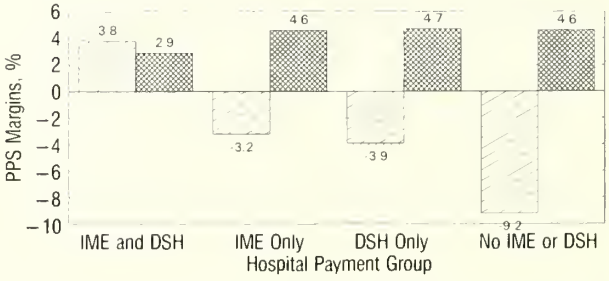

Figure 8.—In the 7th year of the prospective payment system (PPS), hospitals that get both indirect medical education adjustments (IME) and disproportionate share (DSH) payments had the highest PPS (▨) but not total (▩) margins of any hospital group (from ProPAC and the Prospective Payment Assessment Commission).[9(pp52,64)]

Some argue that the IME and other PPS payments can be reduced because average total margins, as opposed to PPS margins, across all types of hospitals are relatively healthy (Figure 8). The average total margin for all hospitals was more than 4% in 1990, but hospitals that receive both IME and disproportionate-share payments continue to have lower total margins (2.9%) than any other group because of their greater number of below-cost and nonpay patients.

Policymakers have argued that once access is expanded through health care reform, IME and PPS adjustments could be reduced or even eliminated without harming teaching hospitals. We disagree with this view and have argued that the purpose of payment for indirect medical education is not to finance uncompensated care, but to recognize factors that legitimately increase costs in teaching hospitals. Even when the health care system is reformed, cost differences between teaching and nonteaching hospitals will continue to exist, and the payment system must recognize this empirical fact through a special adjustment that "levels the playing field" and allows teaching hospitals to compete.

Another unique cost of teaching hospitals that threatens their ability to compete is the direct cost of graduate medical education. These costs include residents' stipends and benefits, salaries and benefits of teaching and supervising faculty, and overhead costs. If the 1980s was the decade of prospective payment systems, the 1990s will be the one of managed care, negotiated rates, and discounted prices. As payers turn toward these new payment mechanisms, some in the academic hospital community have suggested that they could negotiate more effectively if the costs of GME were removed from their operating budgets and were paid separately from a national fund to which all payers would contribute. The question of whether separate streams of revenue will be available to support the many missions of teaching hospitals will continue to be vigorously debated.

At the same time, the federal government is questioning the value it receives for the Medicare dollars it spends —$1.6 billion in 1992—to support its share of the direct costs of graduate medical education. Those who determine Medicare policy have objected to the wide variation in per-resident costs among teaching hospitals. Many fail to understand that at some institutions, faculty in clinical departments depend more on the hospital than on the university for their support. More important, both the Clinton Administration and Congress are frustrated that the medical education community has not met the nation's need for primary care physicians. As their frustration increases, specific suggestions for providing disincentives for nongeneralist training have been proposed. Some would reduce the present support for specialty training by making differential per-resident payments based on specialty. Payments for residents would be weighted more heavily toward trainees in primary care programs such as general internal medicine, pediatrics, and family medicine than for residents in nongeneralist specialties. Some proposals would mandate higher stipends for primary care residents, and others would reduce the variation in direct GME payments. Some proposals recommend channeling GME funds through local consortia that might be more responsive to health professions planning objectives.

We at the Association of American Medical Colleges have opposed proposals to change Medicare direct GME payments, but it is uncertain whether our position will continue to carry the day. The Physician Payment Review Commission and the Prospective Payment Assessment Commission are studying direct GME payments, and both bodies will make recommendations this year that will be taken seriously by the policymakers. We have pointed out that as long as there are unfilled primary care residency positions, proposals to weight hospital payments are unlikely to work. There is also no evidence that medical students' specialty choices are influenced by the level of hospital payments. These proposals have the potential to cause divisiveness within an institution because there will be pressure from disciplines such as emergency medicine, child psychiatry, and physical medicine to be subsumed under the primary care umbrella.

Pressure to reduce the growth in both public and private payers' payments for health care and to redress the physician specialty imbalance will increase in the months and even years ahead. The academic medicine community needs to identify constructive avenues for change.

Physician Payment

In addition to changes proposed for Medicare reimbursement to teaching hospitals, substantial changes have occurred with the introduction of the Medicare fee schedule—the resource-based relative value system. There has been a growing national dependence on practice plan revenues to sustain the basic programs of the medical school. In fiscal year 1990-1991, practice plan income represented an average of 31.4% of medical schools' operating revenue. In some schools, this may be as high as 40% to 50%. Deans across the country are concerned that this fee schedule will result in declining professional fee income that, in turn, will translate into less income for medical schools. This is likely to happen.

By design, the Medicare fee schedule, through the use of a resource-based relative value system, was intended to provide a more equitable way to pay physicians and to eliminate incentives to enter lucrative specialties by paying more for evaluation and management services and less for procedural services. It was also intended to reduce payment to physicians in overpriced urban areas and to reduce the use of technologic procedures, which many think are done to excess. The gains in payment to primary care physicians for historically undervalued evaluation and management services have been disappointing, and one can only conclude that the Medicare fee schedule provides a limited incentive for medical students to select a primary care career.

The effect of the Medicare fee schedule on physician income is highly dependent on the variables of service mix and geographic location. Impact simulations done by

the Physician Payment Review Commission and the Health Care Financing Administration demonstrate that many faculty practice plans will lose substantial revenue under the Medicare fee schedule. Academic physicians, in particular, fit the profile of the "losing" physician. For the most part, they are procedurally oriented and typically are located in an urban area where physician charges have historically been high.

There are also a number of payment policy issues and technical problems with the fee schedule that remain to be resolved. These are arcane, and to discuss them knowledgeably requires a presentation in greater detail than can be covered in this article. Let us merely highlight a few issues of concern.

First, adjustments are needed to account for differences in case complexity and patient severity. Although the Medicare prospective payment system for hospitals adjusts for severity of illness of patients treated in teaching institutions, the Medicare fee schedule does not. Payment to critical care physicians who may spend many hours at the bedside without adequate remuneration is a case in point.

A second major issue is the method for calculating the practice expense component of the fee schedule, using a resource-based approach. Implementing the resource-based method will result in additional cuts in payments for surgical services and may seriously jeopardize the financial stability of many academic practice plans.

A third issue is the Medicare Volume Performance Standard on which the annual update of physician fees is based. The Medicare Volume Performance Standard was intended to provide physicians with a "collective incentive" to keep Medicare expenditures within a targeted national level each year. Should aggregate physician expenditures go above Medicare's standard, fee updates for the subsequent year would be lowered to offset the rise in volume. The major concern with the volume performance standard is that the volume estimates provided Congress by the Physician Payment Review Commission and the Health Care Financing Administration do not accurately reflect the volume and intensity of physicians' practice that is often beyond the control of individual physicians. In addition to the apparent inaccuracy of the volume estimates, the current national scope of the performance standards provides little, if any, incentive to individual physicians or to even large physician groups to modify their behavior if they feel that they have little or no effect on meeting the overall national standard. An alternative approach recommended by the Physician Payment Review Commission is the development of different performance standards for "qualified" groups of physicians. These groups would allow physicians to receive payment updates based on their own performance rather than on the performance of physicians in general. Coupled with the right incentives to practice efficiently, this may be a more worthwhile course than a national performance standard.

There appears to be a fair amount of interest in having third-party payers adopt the Medicare fee schedule. Expanding the fee schedule to private payers would effectively redress the pricing of services and procedures by applying a more rational and scientific approach to the payment of physicians.

Department of Veterans Affairs

In a 1946 Veterans Administration (VA) policy memorandum, the affiliation between VA hospitals (now called medical centers) and medical schools was established.[10] The memorandum lays out the responsibilities of all involved parties, including the Veterans Administration (now Department of Veterans Affairs), schools of medicine, hospital managers, chiefs of service, part-time attending staff, and consultants. This policy memorandum represented an interesting blend of realism, trust, and faith.

From this hopeful beginning the affiliation agreements between medical schools and VA medical centers have expanded so that now 139 VA hospitals and 103 medical schools are incorporated into the system. Each year 22,000 medical students and 30,000 residents receive a portion of their clinical training at VA hospitals.

There are some who now question whether the statement in the original policy memorandum that "there can be no doubt of the good faith of both parties" is still accurate. There is increasing skepticism about what the VA receives from its medical school affiliations and concerns about the quality and quantity of supervision provided to young physicians being trained in VA medical centers, an issue that strikes at the very heart of quality care. Medical schools are perceived as using their "muscle" to reorganize VA medical centers to conform to their own interests rather than to the interests of the veterans being served.

We must recognize that the VA health care system is in trouble. The changing demographics of the veteran population being served dictate the need for change. A fundamental mismatch exists between the location of veterans and the location of the VA facilities. Former Secretary for Veterans Affairs Edward Derwinski tried to address this problem for two rural hospitals in medically underserved areas when he supported the opening of those facilities to nonveterans in the local population. Proponents of the plan saw it as a way to integrate the VA system with its surrounding community more closely by matching the "excess capacity" of the VA system with the communities' scarce supply of health care resources. The proposal was vigorously opposed by veterans service organizations and their Capitol Hill supporters and ended up costing Mr Derwinski his job.

Another worrisome issue that has conspired to drive a wedge between VA medical centers and their academic partners has been a progressive lack of resources in the VA centers. Because of continued budgetary constraints, there are now major shortages in medical staff, nursing, support staff, and equipment. This dearth of resources has caused disenchantment on the part of faculty, residents, and students assigned to work at these centers. Moreover, the erosion of the research budget by inflation has made VA service progressively less attractive to academic physicians. While medical school deans may threaten to

break off affiliations with their VA hospitals, for many that is not a viable option.

Reason tells us that the future of the VA health care system must be tenuous. If serious efforts are made to develop a national health care system with universal access, the role of the VA in such a system must be explicitly addressed. Senator Jay Rockefeller (Democrat, West Virginia) has positioned himself in a dual role as chair of both the Veterans Affairs Committee and the Health Subcommittee of the Finance Committee to ensure that such an examination takes place.

Conclusion

There will always be a link between academic medical centers and the federal government, but the nature of the relationship must change as political leadership, budget priorities, and programmatic initiatives change. President Clinton's commitment to health care reform and cost containment, to economic revitalization, and to deficit reduction dictates that the programs that have inextricably bound academic medical centers to the federal government since World War II will be examined. Whether those commitments will be renewed, restructured, or repudiated is uncertain.

The evolving social contract that our institutions have with our citizens seems to be changing. What is important now is not only the value of our institutions, but the value of the service they provide to society. Accountability, return on investment, pragmatism, and problem solving are the watchwords of today's social contract. The key for academic medical centers is to be flexible, to recognize the need for change, and to accommodate to the changes demanded by the society in which we live. If we accept the need to change, the firm link between government and academic medical centers that has benefited both parties will surely be strengthened; if we adhere doggedly to the status quo, we will see the link come asunder. In his Inaugural Address President Clinton said it best:

> *Profound and powerful forces are shaking and remaking our world, and the urgent question of our time is whether we can make change our friend and not our enemy.*

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Editorials

Regression of Atherosclerosis—An Ounce of Prevention

ELSEWHERE IN THIS ISSUE, Blankenhorn and Hodis summarize the findings of a quarter century of clinical investigation into the possibility that atherosclerotic arterial obstruction may be reversed or regressed.[1] To date, the arteriogram has been the principal tool used to address this question in patients. But as Blankenhorn and Hodis point out, the underlying pathologic processes are complex. Furthermore, the arteriogram is not useful for resolving the biologic and structural processes resulting in clinical disease or for deciphering those mechanisms accounting for the beneficial effects of therapy. To begin to understand the clinical relevance of atherosclerosis regression, we must integrate information and ideas from many sources and disciplines besides angiography—from autopsies, from cell biology and experimental pathology, and from epidemiology, pharmacology, and metabolism, among others.

Current knowledge about atherosclerosis regression comes largely from experiments in animals and from clinical arteriographic studies. The basic term regression implies one thing to experimental pathologists and another to clinicians. To pathologists, regression means the shrinkage of intimal plaque through a reduction in its major components: smooth muscle, macrophages, connective tissues, and lipid. To physicians interpreting human disease by its arteriographic appearance, regression is defined as an enlargement in the caliber of the narrowed arterial lumen. Such improvement seldom occurs in the natural course of the disease. Because these arteriographic images do not permit an easy distinction among the various mechanisms of regression, our understanding of the principal process(es) by which it occurs in patients is limited. Regression, so defined, may occur not only by the process of plaque shrinkage but also by a variety of other possible mechanisms. For example, lysis of fully occlusive thrombi or of mural thrombi is commonly seen in the course of unstable ischemic syndromes.[2] Healing may favorably remodel an acutely disrupted plaque.[3] Adaptive enlargement of the underlying arterial architecture can improve arteriographic lumen caliber independently of changes in plaque size.[4] Relaxation of arterial vasomotor tone can similarly enlarge the lumen caliber.[5] The role of the endothelium and the relationship(s) of therapy to its function have been shown to be important in many of these processes.

Thus, the important question is not "does arteriographic regression occur in patients?" (it does), but "can such regression be promoted with a sufficiently great magnitude and frequency to justify a major therapeutic strategy?" Important related questions are "By what mechanism(s) is regression achieved?" and "Does such induced regression provide clinical benefits?" and "If so, by what means?" Although there is no consensus on the answers to these questions, encouraging evidence is emerging.

In the nonhuman primate studies of Armstrong, Small, and colleagues, atherosclerosis has been shown convincingly to regress with lipid-lowering drugs.[6,7] In the typical regression experiment, atherosclerosis is induced by feeding cholesterol to a group of animals. The amount and composition of intimal thickening is subsequently assessed at specified times, using group-averaged chemical and histologic end points. When the animals are returned to their native vegetarian "regression" diet, plasma cholesterol levels fall quickly to normal (140 mg per dl), and the arterial lipid and connective tissue accumulations partially regress over 20 to 40 months.

Not all forms of cholesterol are readily depleted from these cholesterol-rich intimal lesions. The more mobile forms, including cholesteryl esters in foam cells, lipoproteins, and cholesteryl ester droplets, have been shown to diminish in response to reduced plasma cholesterol, but the cholesterol monohydrate crystals of the core lipid region resist mobilization.[7] Histologic measurements show that plaque mass is reduced during regression therapy.[6,7]

Evidence in Humans

Blankenhorn and Hodis provide a complete list of clinical arteriographic studies the results of which suggest that the obstructive process can be retarded or reversed by therapies that result in reduced levels of low-density lipoprotein (LDL)-cholesterol and increased levels of high-density lipoprotein (HDL)-cholesterol. The composite of evidence from these randomized clinical arteriographic trials consistently indicates that existing coronary lesions in untreated patients progressively worsen in severity on average by about 1% stenosis per year.[8] Regression (improvement) is uncommon in the natural course of the disease. Clinical events occur at a rate of about 5% to 10% annually among untreated patients with clinically established coronary disease. By contrast, treating patients intensively with potent lipid-lowering drug and diet combinations has, in many studies, lessened the mean severity of obstruction by about 0.5% stenosis per year. In other studies, lesion progression has been substantially retarded relative to lesions in control patients. These studies generally conclude that such benefit is predicted by favorable alterations in the LDL-:HDL-cholesterol ratio. Even with intensive drug therapy that results in strikingly favorable alterations of the atherogenic lipid profile, regression by an appreciable amount (10% stenosis) occurs infrequently (1 in 3 patients and 1 in 8 diseased arterial segments[8]).

Surprisingly, this modest and infrequently observed regression of arterial obstruction during lipid-lowering therapy is associated with a much more striking reduction in the frequency of clinical cardiovascular events (ischemic death, infarction, or unstable ischemia refractory to medical therapy and requiring revascularizing procedures). For example, in the Familial Atherosclerosis Treatment Study, the incidence of clinical cardiovascular

events (defined as cardiac death, infarction, or revascularization for progressive ischemia refractory to medical therapy) was reduced by 73% with intensive lipid-lowering therapy when compared with a conventional strategy.[9] Of 52 patients randomly assigned to diet and possible colestipol therapy, 10 had such an event, as did 5 of 74 to therapy with either niacin plus colestipol or lovastatin plus colestipol. In the Program on the Surgical Control of the Hyperlipidemias, 838 patients were randomly allocated to partial ileal bypass operation or to usual clinical care.[10] After five years, the ileal bypass group, on average, had a 42% reduction in LDL-cholesterol levels and little change in HDL-cholesterol levels; the usual-care group had an 8% reduction in LDL-cholesterol levels. After ten years, the surgical group had 32 cardiac deaths, 50 nonfatal myocardial infarctions, 52 coronary artery bypass operations, and 15 coronary angioplasties. Corresponding figures in the medically treated group were 44 ($P = .13$), 81 ($P < .001$), 137 ($P < .0001$), and 33 ($P = .005$), respectively. All-cause mortality was reduced 36% ($P = .02$) among the majority with baseline ejection fractions of 0.50 or more. In the St Thomas' Atherosclerosis Regression Study, there were 10 cardiovascular events among 28 patients completing the "usual care" assignment, 3 among 27 completing diet alone ($P < .05$), and 1 among 26 completing diet plus cholestyramine ($P < .01$).[11]

Thus the evidence from angiographic trials demonstrates both coronary artery and clinical benefits from lipid-lowering therapy using any of a variety of treatment regimens. The findings of decreased arterial disease progression and increased regression have been convincing but, at best, modest in their magnitude. In view of these modest arterial benefits, the associated reductions in cardiovascular events have been surprisingly great. On closer examination of the data of the Familial Atherosclerosis Treatment Study, we find that the 73% reduction in the incidence of clinical events in this study is entirely explained by a 93% reduction in the likelihood that a mildly or moderately narrowed arterial segment would substantially progress to become the severe lesion that caused the clinical event.[8] The magnitude of the clinical benefit is best explained in terms of this observation, using the following lines of reasoning[8]:

- Clinical events most commonly spring from lesions that are initially of mild or moderate severity and that abruptly undergo a disruptive transformation to a severe "culprit" lesion.[12]
- The process of plaque fissuring leading to plaque disruption and thrombosis triggers most clinical coronary events.[13] Fissuring is predicted by a large accumulation of core lipid in the plaque and by a high density of lipid-laden macrophages in its thinned fibrous cap.[14] Lesions with these characteristics make up only 10% to 20% of the overall lesion population but account for 80% to 90% of the acute clinical events.
- In the experimental setting, normalization of an atherogenic lipid profile substantially decreases the number of lipid-laden intimal macrophages (foam cells) and gradually depletes cholesterol from the core lipid pool.[6,7] As above, these two aspects of plaque composition are predictors of subsequent plaque instability. Thus a normal lipid profile should result in plaque stability.
- In the clinical setting, intensive lipid-lowering therapy virtually halts the progression of mild and moderate lesions to severe obstructions, thus preventing clinical events.[8,9]

In conclusion, the reduction in clinical events observed in these human arteriographic trials appears to be best explained by the relationship of the lipid and foam cell content of the atherosclerotic plaque to its likelihood of fissuring and by the effects of lipid-lowering therapy on these "high risk" plaque features. The composite of data presented here supports the hypothesis that lipid-lowering therapy selectively depletes lipid (regresses) in that relatively small but dangerous subgroup of "vulnerable" fatty lesions containing a large lipid core and dense clusters of intimal macrophages. By doing so, these lesions are effectively stabilized, and the clinical event rate is accordingly decreased. Thus, in the course of such treatments, this small lessening in overall disease severity and the relatively infrequent occurrence of definite lesion regression represents the "ounce of prevention" that, by stabilizing the vulnerable plaques, far outweighs the "pound of cure" (revascularization, restriction of lifestyle) associated with unnecessary clinical ischemic events.

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Ectopic Pregnancy—Becoming a Nonsurgical Disorder

THE INCIDENCE OF ectopic pregnancy has been gradually rising, accounting for almost 2% of all pregnancies. Ectopic pregnancy has become a leading cause of maternal morbidity and mortality.[1]

Accurate and early diagnosis is essential for the appropriate use of conservative medical and surgical treatment of ectopic pregnancy.[2,3] In appropriate cases, expectant management may be an option. Ectopic pregnancy can become a "nonsurgical disorder" with early nonsurgical diagnosis and medical management with methotrexate in physicians' offices.[4] The effectiveness of methotrexate therapy is enhanced when given early (ectopic mass < 3.5 cm, no fetal cardiac activity, and human chorionic gonadotropin [hCG] level < 15,000 IU per liter [15,000 mIU per ml]).[5] Most women with ectopic pregnancy who are not candidates for methotrexate therapy can be treated surgically through the laparoscope on an outpatient basis.[6] Laparotomy and hospital admission will be necessary in a few patients who are hemodynamically unstable. In addition to minimizing surgical intervention, early diagnosis and treatment may improve fertility following ectopic pregnancy. The cost savings of early diagnosis and treatment could be enormous. Outpatient methotrexate treatment could cost as little as $500 compared with $5,000 to $15,000 for surgical treatment.

Patients with ectopic pregnancies still present with tubal rupture and compromised hemodynamic status and consequently require emergency laparotomy. Both patients and medical staff must be better educated. No diagnostic test is useful until it is ordered. For women who have risk factors for ectopic pregnancy, there must be a high degree of suspicion in the presence of abnormal vaginal bleeding and abdominal pain. A sensitive hCG assay must be done as soon as pregnancy is suspected. Primary care and emergency department physicians must also have a high degree of suspicion and diligently observe high-risk patients during early pregnancy.

A single quantitation of hCG cannot be used to separate ectopic versus normal pregnancies unless correlated with an ultrasonogram of the pelvis. The major value of hCG levels is in establishing discriminatory zones when ultrasonography can be used to rule out intrauterine pregnancy. Physicians must establish their own discriminatory zone. Factors affecting minimum values of hCG needed to visualize an intrauterine pregnancy include the reference standard for hCG levels, abdominal versus vaginal ultrasonography,[7] and ultrasonographic experience. Serial quantitative hCG titers have become the standard for assessing viability in early pregnancy, with a rate of rise of less than 66% over 48 hours in most nonviable pregnancies. Because as many as 20% of ectopic pregnancies can have normally rising hCG titers, serial hCG titers are often used to determine when a discriminatory level of hCG is reached to appropriately time an ultrasound examination. Extra care is needed to interpret hCG values in patients at high risk for multiple pregnancy (ovulation induction and in vitro fertilization). The demise of one twin may result in temporary plateauing or falling of hCG levels with the remaining twin surviving.

Ultrasonography is used most often to exclude ectopic pregnancy by diagnosing an intrauterine gestational sac; the likelihood of both an intrauterine and ectopic pregnancy is only 1 in 30,000. As ultrasound technology and skill improve, an increasing number of ectopic pregnancies (as many as 70%) can be visualized by ultrasonography. Vaginal sonography has lowered the discriminatory zone for hCG (1,000 to 2,000 IU per liter for vaginal and 6,000 to 6,500 IU per liter for abdominal), thus lowering the gestational age at diagnosis. Vaginal sonography is also used to assess additional adnexal disorders (ovarian cysts and hydrosalpinx), the presence of fluid in the peritoneal cavity, the presence of fetal cardiac activity, and the size of the ectopic pregnancy. All of these sonographic findings will influence the selection of appropriate treatment.

Because serial hCG assessment results in a 48-hour delay in the diagnosis, the single assessment of serum progesterone concentrations has been used to assess fetal viability. A high predictive value is associated with progesterone values of more than 80 nmol per liter (25 ng per ml) for viable and less than 16 nmol per liter (5 ng per ml) for nonviable fetuses.[8] Patients with progesterone concentrations of less than 80 nmol per liter may benefit from ultrasonic evaluation to increase the likelihood of the early diagnosis of ectopic pregnancy. Because of considerable assay variation, each laboratory will have to establish its own threshold values. The progesterone level is of little value in differentiating early miscarriage from ectopic pregnancy.

There may be no role for culdocentesis in the contemporary diagnosis and management of ectopic pregnancy.[9] Culdocentesis is a painful, invasive, nonspecific test that adds little if the above test results are available quickly and accurately. A hemodynamically unstable patient with fluid found in the peritoneal cavity by ultrasonography needs prompt surgical treatment whether or not blood is found on culdocentesis. The presence of blood on culdocentesis in a hemodynamically stable patient does not obviate expectant management (transiently bleeding corpus luteum cyst) or medical or laparoscopic management in appropriate patients.

The cornerstones of the early diagnosis of ectopic pregnancy remain a high index of suspicion, sensitive quantitative hCG assay, and transvaginal pelvic ultrasonography. The widespread use of existing diagnostic

and therapeutic techniques could markedly decrease the adverse effects of ectopic pregnancy on women's health.

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Government and Academic Health Science Centers

THIS ISSUE of THE WESTERN JOURNAL OF MEDICINE contains a thoughtful analysis of the many ways in which the national government interacts with and influences the functions of academic health science centers in the United States.[1] The authors, as seasoned senior officers of the Association of American Medical Colleges (AAMC), are exceptionally well informed about these interactions. In fact, it is not by happenstance that the AAMC moved its headquarters from Chicago to Washington, DC, some years ago. The groves of academe, at least in medicine, are no longer tranquil sites for detached scholarship. The imperatives of public policy increasingly intrude, seduce, and command, and the pace of these incursions is accelerating.

This is perhaps not surprising. Academic health science centers are unique in the university in that they are directly involved in running a major industry, that of health care. In all of its other activities the university maintains a well-defined boundary between its academic activities and the workaday world beyond. Schools of medicine, however, participate directly in the industry of health care; it is impossible to ascertain a phase transition between those of their activities that are "academic" and those that are not.

"The health of all the people is really the foundation upon which all their happiness and all their powers as a state depend." Few would dispute the validity of this spacious statement by Disraeli. Nevertheless, the responsibility of the government in assuring access to health care has been accepted fitfully and by slow accretion in this country, much more slowly than in any other so-called developed countries of the world. We are currently lurching further along that pathway with all of the noise and turmoil of the political process. Along with the rest of the medical care system, academic health science centers are being buffeted in this transition, as has been well documented in the review by Petersdorf and Turner.

Academic health science centers educate the next generation of health professionals, directly supply patient care, conduct biomedical research, and render community service. The range of these activities mandates large and complex organizations, with uneasy mingling of the function of the university and of the health care industry. Academic health science centers are therefore highly susceptible to changes in policy and resource allocations in either the university or in the public arena. This vulnerability underlies the choice of title for the current review, "Academe and Government—Firm Link or Broken Reed?" Clearly the link is not firm, but perhaps the reed is only bent rather than broken. Let us hope that it maintains its resiliency to spring back.

A key role of academic health science centers is to conduct biomedical research. Biomedical research is patient care one step removed. In recognition of this, the government allocates approximately $10 billion a year for the support of research, about $40 a year for each citizen. This is a form of national defense, not against external adversaries, but against the implacable, internal adversaries of disease and disability that affect us all, now or in the future. Is it enough? The answer is of necessity a subjective one.

The investment has been enough to ensure the supremacy of the United States in the revolution in biological science that has characterized the last half of the 20th century and in the application of that science to the study of human diseases. The secrets of DNA, formerly locked in nuclear silence, can now be read as an antique and universal language that spells out the structure and function of all living things. Almost weekly, reports appear that elucidate the pathogenesis of genetic disorders as misprints, omissions, or even stuttering in that language of purine and pyrimidine bases strung along a sugar phosphate backbone. A single scientific discovery, that of recombinant DNA technology, has not only revolutionized biology, it has spawned a whole new industry. The annual economic activity of that biotechnology industry alone will shortly exceed the total government investment in biomedical research over the past decade. The return on the national investment in research has clearly been a magnificent achievement and a splendid legacy for the future.

Is it enough? Even in the face of these past prodigies, there is a serious current crisis in biomedical research. We have educated a new generation of basic scientists and physician-scientists who are poised to exploit the opportunities of the new biological sciences. Now, however, the success rate for funding projects that have been approved by stringent peer review as being scientifically meritorious has fallen discouragingly low, often less than one in five. Opportunities are being lost or delayed. Only slightly more than 1% of the national health care budget is being spent to "improve the product," that of health sci-

ence and technology. This form of national defense is being seriously neglected at a time when it has the most to offer.

Abba Eban said that he believed that both men and nations always acted in a rational fashion—once they had exhausted all other possibilities. In the political frenzy of changing our health care system, let us hope that the academic health science centers can continue to produce not only the next generation of health care professionals but also the science and technology that will ensure their effectiveness.

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A Crisis in Medical Education—One Person's Concern

SOME TIME AGO I applied to and gained entrance into medical school. Coming from a small midwestern town, I was inspired by several local physicians whose concern for their patients and for the community was well known. I progressed through medical school, entered residency and, ultimately, fellowship. During those years my goals changed somewhat, and I decided to focus my efforts in a limited area to become expert in at least one field of knowledge. Then I realized I wanted to teach medicine and sought a career in academics. Over the years my impressions of academia were molded and remolded by the prevalent academic climate. I saw changes and more changes and became increasingly aware of the pressures on academic physicians and medical centers. Now I am concerned that to survive, these faculty and these institutions are going to have to engage in activities that will compromise their ability to perform their academic mission. In fact, if current trends continue, we will legitimately be asking who is going to teach the medical students.

What pressures exist in academia that detract from the mission to teach medical students? The first is the obvious and much-discussed issue of research. Research is essential to all medical schools. It is the life blood of the institutions and is part of the teaching mission. It is a way of advancing knowledge and providing new and innovative methods for future implementation. The thrill of the research endeavor is often the glue that binds our best faculty to academia. Research itself is not the problem. The difficulty now confronting academic centers is the pursuit of research funding. To be competitive now, investigators must spend increasing time locating funding sources. In addition, they must stay at the critical edge of research to maintain their funding, requiring that they devote increasing efforts to their studies and less time and interest to instructing medical students. The quest for new knowledge has required the development of newer technologies that can unveil the secrets of the individual cell down to the molecular level. Acquiring and maintaining competence in these new methods has required a further commitment and has additionally compromised the time available for clinical instruction.

While the requirement for basic research demands increasing time and effort, medical schools are caught in even more compromising struggles: competing for patients and generating funding to underwrite the costs of their hospitals and clinics. With the expanding of managed care, many medical schools are in danger of losing their clinic populations to institutions that can provide care in a more cost-competitive way because they do not have to underwrite the costs of education. With more restricted public funding available for the poor, managed care contracts are being considered as a means of reducing the cost of caring for the underfunded. Academic centers may have to compete for their teaching patients. To compete effectively, the care of these patients may well have to be managed by highly trained physicians. These skilled physicians not only will have to provide the least costly care but will have to spend most of their time doing this. Senior clinicians may be required to spend more time in direct patient care, leaving less time for teaching.

The private patients with insurance who previously brought insurance payments to balance the ledgers of the academic centers are now fewer in number, and those who remain are often being diverted to other institutions. The competition for these patients is requiring academic centers to focus more on service and less on teaching.

If we have full-time researchers going in one direction and full-time clinicians in another, who will teach the medical students? It is clear they must be taught. With the current emphasis on containing costs, good clinical judgment, effective clinical decision making, and useful clinical algorithms will be at a premium. These processes must be taught. They will become as important to clinicians as the techniques of molecular biology are to basic researchers. Even more critical to the success of the entire medical industry is the notion that cost containment and good clinical judgment are opposite sides of the same coin.

Acknowledging that clinical skills and the process of clinical decision making will have to be taught, how will this be accomplished? Medical schools will have to support a certain number of dedicated teachers—persons who will be hired to ensure that the principles of clinical medicine are imparted to the students. For these faculty a system of rewards must be developed to allow for their promotion and tenure. But with rising costs and diminishing budgets, especially if Medicare teaching supplements are decreased by the federal government, these teachers will be in short supply. Perhaps the major consumers of physician supply such as large health maintenance organizations will have to endow additional positions for teaching faculty to establish a critical mass.

Other resources will have to be used. A highly selected group of practitioners may have to be awarded meaningful clinical titles that will serve to distinguish them and add to their prestige in the community. They in turn will teach a certain number of hours to assist in the training of future clinicians. Other honors, including fi-

nancial benefits, may have to be awarded these part-time clinician teachers. What should be different about some of these clinician teachers from those seen in some of the systems in place today will be a more intense process of selection and a greater system of awards that allows for more prestige and greater distinction. Other resources may also have to be identified to obtain an adequate number of teachers, but the search must continue because future physicians and future patients will require that the best of clinical knowledge and experience be imparted from generation to generation to allow our children and our children's children to get the best medical care possible.

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EDITOR'S NOTE: *Dr Cesario received the 1993 Golden Apple Award presented by the California Medical Association to recognize exceptional physicians who have made a lifelong commitment to teaching.*

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Educating Physicians for International Health

To the Editor: The International Health Medical Education Consortium (IHMEC) strongly concurs with Sir Gordon Wolstenholme's call for improving basic health and access to primary health care worldwide to promote self-help, economic independence, and social stability.[1] The case for establishing true primary care for the world's population has long been compelling. Daily, 40,000 children die from ordinary malnutrition and preventable disease and one woman per minute worldwide from problems of pregnancy and childbirth. Despite progress in providing immunizations, devastating shortfalls in basic primary care, safe water and sanitation, primary education and literacy, and safe motherhood remain. The price of closing these gaps is shockingly low—only $25 billion a year according to UNICEF estimates, compared to the annual outlay of $50 billion in Europe for cigarettes or $31 billion in the United States for beer. As little as 3% of all bilateral aid currently goes to primary health care and family planning.

In the United States, the cracks in our primary care system have become evident to rich and poor alike: 37 million Americans are underinsured, and approximately 10% of our children lack a primary care provider. Only 57% of our 2-year-olds are up to date on their immunizations. Moreover, as pointed out by Morgan and Mutalik[2] at the National Council for International Health, "International health has come home." Official immigration accounted for 30% of population growth in the United States in the 1980s, heightening the disproportionate effect of inadequate primary care falling on the ethnic poor.

Our mission at IHMEC is medical education to improve health and equity in access to health care throughout the world. Our organization was launched in June 1990 to link faculty teaching international health in North American medical schools. We are committed to bringing core skills in primary care and community health assessment for underserved United States and third world communities into the mainstream of US medical training. Our goals are the following:

- Strengthen the teaching of international health at all levels of training, including curriculum development for effective cross-cultural health care.
- Establish an IHMEC network of clinical sites overseas and standards for selection of both trainees and sites.
- Develop stronger career tracks for students, residents, and faculty involved in international health training and programs.
- Provide an ongoing forum for members to share expertise, develop policies, and establish liaison with other organizations interested in international health medical education issues.
- Facilitate collaborative training relationships with students and faculty in foreign medical schools.

Currently IHMEC has over 100 members representing approximately 68 of the 126 medical schools in the United States. Over 200 faculty and health professionals are on IHMEC's mailing list. Membership is open to any faculty member affiliated with a North American medical school. Annual meetings are scheduled to coincide with the meeting of the American Association of Medical Colleges each November.

We would be pleased to join forces with other interested health care professionals both in the United States and abroad.

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False-Positive Human Immunodeficiency Virus Type I ELISA Results in Low-Risk Subjects

To the Editor: An increasing number of patients with few or no risk factors for human immunodeficiency virus (HIV) infection are asking physicians to screen them for the presence of HIV antibodies. The most commonly used screening method is the enzyme-linked immunosorbent assay (ELISA) test. This test is inexpensive, yet has a relatively high degree of both specificity and sensitivity. We report the results of our recent screening of low-risk healthy subjects who volunteered to participate in research at the University of California, San Diego, using the Organon Vironostika Microelisa Kit (Organon Teknika Corporation, Durham, North Carolina). Although this kit is reported to have a specificity of 98.2% and a false-positive rate of 0.58%, we have received distressingly higher results (manufacturer's package insert). During a ten-month period, 3 of 77 low-risk normal controls had positive ELISA tests. Subsequent Western blot analyses and follow-up ELISA tests were negative. This gives a false-positive rate of about 4%.

Report of Cases

Case 1. The patient, a 38-year-old woman who had had unprotected anal intercourse twice in her life, tested strongly positive for the presence of HIV-1 antibodies. Further questioning revealed that she had had an outbreak of herpes simplex type 2 infection three weeks before her baseline laboratory evaluation.

Case 2. This patient, a 23-year-old man with no known risk factors, tested positive for the presence of

HIV-1 antibodies. A careful review of his medical history revealed that he had been inoculated with the influenza vaccine two months before testing and was having a mild upper respiratory tract infection at the time the initial blood specimen was drawn.

Case 3. The patient, a 32-year-old man, had no known HIV risk factors, but he had received the influenza vaccine two months before HIV testing. He also had had hepatitis C infection several years previously.

These cases illustrate that although the ELISA test may be extremely sensitive, it has varying degrees of specificity. The false-positive ELISA tests in these cases were probably due to cross-reactive immunoglobulin (Ig) M antibodies produced to other viral epitopes. These IgM antibodies may nonspecifically bind to the ELISA microplate and react with anti-idiotype antibodies to cause a false-positive reaction.

Although positive ELISA tests are routinely confirmed with a Western blot test for the HIV antibody, at our institution (and others) there is frequently a considerable delay from the time that the initial ELISA result is known to when the result of the Western blot test is available. Therefore, as part of the screening of low-risk persons, we now take a careful history specifically asking about recent viral infection and exposure to viral vaccines. Anyone giving such a history we then proactively warn that there is a risk of a false-positive ELISA result. Since instituting this policy six months ago, we have screened another 50 subjects and have had two more false-positive ELISA results; both our and our patients' anxieties were greatly diminished by the proactive discussion.

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* * *

Manufacturer Responds

To the Editor: With regard to Challakere and Rapaport's letter on false-positive ELISA results in low-risk populations, we offer the following response. The Vironostika HIV-1 Microelisa System produced by Organon Teknika Corporation has a specificity claim of 99.96% based on the testing of subjects from a low-risk population (not the 98.2% figure stated in the letter). Despite the manufacturer's attempts to maintain the highest specificity when an HIV test has been pushed as it is for maximum sensitivity, there will be occasions when there are biological false-positives. Supplemental tests are a critical part in testing algorithms to resolve true- from false-positives. For instance, during the 1992 flu vaccine season there were reports of some vaccinee sera that were reactive with HIV ELISA assays but were completely negative in HIV Western blot assays. Organon Teknika Corporation made presentations at two Food and Drug Administration (FDA) panel advisory boards to discuss this type of false reactivity and to report results on modifications to the VirHIV-1 ELISA test that would eliminate this reactivity and improve specificity. The license amendment for this modified test is under FDA review.

J. W. D. KAY, PhD
HIV Program Director
Organon Teknika Corporation
100 Akzo Ave
Durham, NC 27712

The Resurgence of Saccharin

To the Editor: Approximately 60 million adults in the United States complain of indigestion or heartburn at least once a month.[1(p2)] To treat this potentially lucrative patient base, pharmaceutical companies have introduced a variety of antacid preparations.

Although there has been a plethora of rhetoric on which formula is the best, no comment has been made on the addition of a declared hazardous chemical to these new flavored antacid preparations—sodium saccharin.

While a single tablet or liquid dose contains only a small amount of the sweetener, a recommendation of up to 24 tablets or 12 teaspoons a day over 24 hours must be considered a potential risk factor for long-term use.

In 1977, in compliance with the Delaney Act,[2] the US Food and Drug Administration (FDA) proposed a ban on saccharin as a food additive because of evidence of carcinogenicity in animals.[3] Congressional action blocked the ban and final FDA regulations are still pending.[4]

After a lengthy and stormy national debate, saccharin was removed from most soft drinks, foods, and pharmaceuticals. A total elimination of the product was never accomplished, however. The public continues to be exposed daily to saccharin in a limited number of products such as toothpaste, mouthwashes, thirst quenchers, cold and cough preparations, dietetic foods, and sweeteners.

Even though the government has continued to authorize the restricted use of saccharin, public acceptance and sales have declined in recent years because of health concerns and the introduction of several other thoroughly tested artificial sweeteners. But this trend may be reversing with the introduction of saccharin into newly formulated antacid, analgesic, antidiarrheal, laxative, and cold and cough preparations.

Although federal regulatory codes have mandated that manufacturers place a hazardous substance warning on each saccharin-containing food package and retail establishments must prominently display "saccharin notices" in designated areas, similar notices—which have serious deleterious effects on product merchandising—are not required for non-food or drug items. Why regulators have not demanded that manufacturers use alternative, readily available taste enhancers, especially in tablet forms, also remains a mystery.

As more and more modified-flavor formulas are released, the FDA continues to avoid public comment on

the resurgence of saccharin. The propriety of subjecting humans to an agent that produces cancer in animals solely for marketing a larger choice of products must be re-evaluated.

HOWARD H. FRANKEL, MD, PhD
6651 Cory Dr
Huntington Beach, CA 92647-5662

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Correction

The captions to Figures 4 and 5 on page 587 of the Gelber article on "Hansen's Disease" (June 1993; 158:583-590) were switched during the production process. The caption for Figure 4 should read "The dermis in lepromatous leprosy shows foam cells (hematoxylin and eosin stain)." The caption for Figure 5 should read "An acid-fast stain of the dermis in untreated lepromatous leprosy shows the numerous clustered bacilli, or globi."

The Editors are pleased to receive letters commenting on articles published in the journal in the past six months, as well as information or short case reports of interest to our readers. ALL MATERIAL SUBMITTED FOR CONSIDERATION MUST BE DOUBLE-SPACED. Letters NO LONGER THAN 500 WORDS are preferred. An original typescript and one copy should be submitted. All letters are published at the discretion of the Editors and subject to appropriate editing. Those of a scientific nature will be peer reviewed. Authors should include information regarding conflict of interest, when appropriate ("I warrant that I have no financial interest in the drugs, devices, or procedures described in this letter"). Most letters regarding a previously published article will be sent to the authors of the article for comment. Authors of accepted letters will have an opportunity to review the edited version before publication.

Lessons From the Practice

The Town Doctor—A Remembrance

DAVID A. FISHER, MD, *Antioch, California*

The time was shortly after the Second World War. Father, a small town physician, had recently come home from the Army. Life in Westwood, Massachusetts, was slow, even drowsy, more an extension of the 19th century than a part of the 20th. The area was still semirural, presuburban in an era of barns, carriage houses, and one-car garages.

My father's day started with giving 7 AM anesthesia at the modest brick hospital in a nearby industrial town. Then followed hospital rounds and a return to the house, a quick cup of coffee, and a look at the list of patients to be seen—a roster dutifully and meticulously compiled by Mother, his office manager, secretary, receptionist, and cleaning service. After hospital duties he would visit, with his black bag, five, ten, or more patients before returning home for a quick lunch and office hours in three well-equipped rooms on the other side of the house. Father had no nurse, for an office nurse was a luxury affordable only by affluent city physicians and specialists.

In 1946 no one made appointments. The patients came and waited to be seen on a first-come, first-served basis. His notes, hardly legible, would have modern-day chart auditors apoplectic. A diagnosis: flu, varicella, OM, pneumonia RLL, and the treatment: digitalis leaf, mercurhydrin, Gantrisin, ASA with codeine. But the patients got superb treatment by this kind, dedicated, diligent physician. After office hours, he would make a house call or two concerning some urgent matters, have supper, hold evening hours from 7 to 8:30, pay a quick visit to the hospital, and come home and go to bed. Often after he went to bed, the phone would shatter the nocturnal quiet, and he would dash out into the night for an emergency house or hospital visit or delivery. His energy, stamina, and cheerful disposition ("oslerian aequanimitas") were awe-inspiring to his youthful worshipper.

I remember most the house calls: all those names carefully annotated in a maroon appointment book. Some had a check mark indicating that the family had paid, many an "O" meaning to be billed, and not a few with an "X" signifying payment reduced with an adjacent single digit inscribed. Day after day, Saturdays, Sundays, torpid summer days, snowy winter nights, the small town doctor made his rounds. When there was an auto or farm accident, the fire department would call; during a snowstorm the town snowplow would clear the driveway, and a worker would put on the car chains, for here was an important service, a resource to be maintained, even nurtured.

People in the town all knew him as their friend, their confidant, a man of science and wisdom, a village minister who had visited them in the cherished intimacy of their own homes. He would tell me that if you truly want to know a person, to understand him or her, observe the person at home, in relationship with the family, pets, house, bedroom, garden, furniture, laundry in the washtub, dishes in the sink, and cooking odors.

After almost 50 years and how many thousand house calls, Dad retired. Well into his 70s, he was still vigorous of body and keen of mind, chasing out into the Massachusetts nights to attend a youngster with croup or an old-timer who had developed cardiac failure or, sadly, to pronounce death. His eyes had developed glaucoma. Achilles had his tendon, Father his eyes. Night driving became difficult, even unsafe. To him the practice of medicine rested on the tripod of hospital activities, office visits, and house calls. A two-legged stool cannot stand. Dad sold his practice for a small amount to a bright young Harvard-trained internist who did not make house calls, remained three years, and left for medical administration.

More than 1,000 people attended Dad's retirement tea. A Boston television station did a segment on the retirement of a "country doctor." The television reporter called at the door and asked Mother where he was. He was on a house call, his last patient visit.

Recently we visited Father and accompanied him on his robust daily constitutional. My wife and I tried to keep up with him on that drizzly March day. As we walked, he said, a bit wistfully, "I have visited the people in every one of these houses. Quite an education."

* * *

"Lessons From the Practice" presents a personal experience of practicing physicians, residents, and medical students that made a lasting impression on the author. These pieces will speak to the art of medicine and to the primary goals of medical practice—to heal and to care for others. Physicians interested in contributing to the series are encouraged to submit their "lessons" to the series' editors.

JONATHAN E. RODNICK, MD
STEPHEN J. McPHEE, MD
Assistant Editors

(Fisher DA: The town doctor—A remembrance. West J Med 1993; 159:217)

From the Department of Dermatology, University of California, San Francisco, School of Medicine, and University of California, Davis, School of Medicine.
Reprint requests to David A. Fisher, MD, 3701 Lone Tree Way, Ste 6, Antioch, CA 94509.

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Be a good listener. Even if you are hassled beyond belief, a patient should feel the intensity of your undivided attention and should sense that you have absolutely nothing else to do but to hear his or her story.

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And, above all, be kind, not only to your patients and their families, but to your colleague physicians and nurses, to those around you who are part of the health care team, and to those who toil as part of the support for what you do.

Finally, you are the stuff and substance of this extraordinary school and hospital. What you are, it will be.

Good luck to all of you.

JOHN E. FENN, MD
Chief of Staff
Yale-New Haven Hospital
New Haven, Connecticut

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(Continued on Page 225)

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(Continued from Page 224)

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NORTHERN CALIFORNIA HOSPITAL seeking a BC/BE Internist to staff its new satellite medical clinics. Assistance is available in establishing a practice. Net income guarantees are open including support for office staff and required equipment. Contact Margaret Ward, Redbud Community Hospital, PO Box 6720, Clearlake, CA 95422; (707) 994-6486, ext 128.

SEATTLE. Pacific Medical Center and Clinics has Family Practitioner BC/BE positions available at three of its six neighborhood clinics. PMC is a large multispecialty nonprofit organization affiliated with the University of Washington. Our patient population includes retired military personnel and their families, managed care patients involved in PPOs and HMOs, and fee-for-service patients. Most of our well run, well equipped clinics are located within one mile of a major hospital. PMC offers its providers a balanced lifestyle, competitive salaries and an excellent benefit package that includes a competitive salary, pension plan, bonus plan, paid malpractice, plus much more. Come enjoy the Puget Sound area with all it has to offer. Send CV to Marilyn Gosanko, Employment Manager, Pacific Medical and Clinics, 1200 12th Ave S., Seattle, WA 98144; (206) 326-4111. EOE.

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MAJESTIC SKAGIT VALLEY IN WESTERN WASHINGTON has multispecialty group seeking eighth Family Practitioner. BC/BE, OB optional. Competitive salary and benefits. If interested, send CV to Shane Spray, 1400 E Kincaid, Mount Vernon, WA 98273.

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UNIVERSITY PHYSICIAN. Student Health Service, University of Wyoming, Laramie is seeking a physician for full-time employment. Applicants must have an MD degree plus be BC/BE by either AAFP or American Board of Internal Medicine. Must have a license or qualify for licensure to practice medicine in the state of Wyoming. Prefer candidate to have at least four years of Primary Care experience. Physician will join three full-time physicians to care for 10,000 students on the campus at Laramie, Wyoming. The Student Health Service has its own laboratory, x-ray, and pharmacy. Salary commensurate with qualifications and experience. Closing date is 10/6/93 or until position is filled. Inquiries can be made to Albert H. Roth, MD, Director, Student Health Service, University of Wyoming, PO Box 3068, Laramie, WY 82071. Send applications and CV to Human Resource Department, PO Box 3422, Laramie, WY 82071. EEO/AA.

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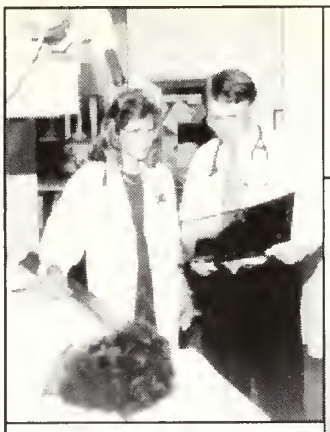

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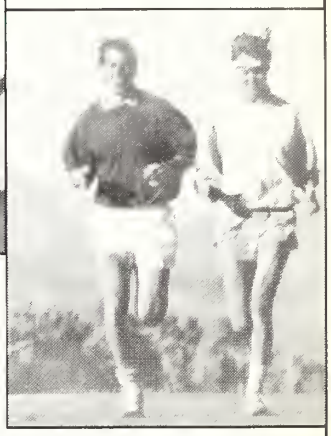

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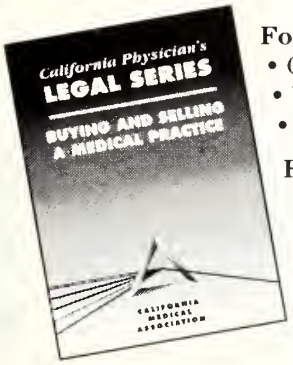

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Wyoming Medical Society–PO Drawer 4009, Cheyenne 82003-4009. (307) 635-2424. Annual Meeting: 1994, date and location to be announced.

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ALTACE™ ramipril

Usual Starting Dose–2.5 mg Once-a-Day*

Available in Easy-to-Swallow Capsules

1.25 mg 2.5 mg 5 mg 10 mg

BRIEF SUMMARY

USE IN PREGNANCY

When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, ALTACE should be discontinued as soon as possible. **See WARNINGS: Fetal/neonatal morbidity and mortality.**

ALTACE is available in potencies of 1.25 mg, 2.5 mg, 5 mg, and 10 mg in color-coded, hard gelatin capsules.

INDICATIONS AND USAGE: ALTACE is indicated for the treatment of hypertension. It may be used alone or in combination with thiazide diuretics.

In using ALTACE, consideration should be given to the fact that another angiotensin converting enzyme inhibitor, captopril, has caused agranulocytosis, particularly in patients with renal impairment or collagen-vascular disease. Available data are insufficient to show that ALTACE does not have a similar risk. (See WARNINGS.)

CONTRAINDICATIONS: ALTACE is contraindicated in patients who are hypersensitive to this product and in patients with history of angioneurotic edema.

WARNINGS: ***Angioedema:*** Angioedema of the face, extremities, lips, tongue, glottis, and larynx has been reported in patients treated with angiotensin converting enzyme inhibitors. Angioedema associated with laryngeal edema can be fatal. If laryngeal stridor or angioedema of the face, tongue, or glottis occurs, treatment with ALTACE should be discontinued and appropriate therapy instituted immediately. **Where there is involvement of the tongue, glottis, or larynx, likely to cause airway obstruction, appropriate therapy, e.g., subcutaneous epinephrine solution 1:1,000 (0.3 mL to 0.5 mL) should be promptly administered.** (See ADVERSE REACTIONS.)

Hypotension: ALTACE can cause symptomatic hypotension, after either the initial dose or a later dose when the dosage has been increased. Like other ACE inhibitors, ramipril has been only rarely associated with hypotension in uncomplicated hypertensive patients. Symptomatic hypotension is most likely to occur in patients who have been volume- and/or salt-depleted as a result of prolonged diuretic therapy, dietary salt restriction, dialysis, diarrhea, or vomiting. Volume and/or salt depletion should be corrected before initiating therapy with ALTACE.

In patients with congestive heart failure, with or without associated renal insufficiency, ACE inhibitor therapy may cause excessive hypotension, which may be associated with oliguria or azotemia and, rarely, with acute renal failure and death. In such patients, ALTACE therapy should be started under close medical supervision; they should be followed closely for the first 2 weeks of treatment and whenever the dose of ramipril or diuretic is increased.

If hypotension occurs, the patient should be placed in a supine position and, if necessary, treated with intravenous infusion of physiological saline. ALTACE treatment usually can be continued following restoration of blood pressure and volume.

Neutropenia/Agranulocytosis: Another angiotensin converting enzyme inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression, rarely in uncomplicated patients, but more frequently in patients with renal impairment, especially if they also have a collagen-vascular disease such as systemic lupus erythematosus or scleroderma. Available data from clinical trials of ramipril are insufficient to show that ramipril does not cause agranulocytosis at similar rates. Monitoring of white blood cell counts should be considered in patients with collagen-vascular disease, especially if the disease is associated with impaired renal function.

Fetal/Neonatal Morbidity and Mortality: ACE inhibitors can cause fetal and neonatal morbidity and death when administered to pregnant women. More than 100 cases have been reported in the world literature. When pregnancy is detected, ACE inhibitors should be discontinued as soon as possible.

The use of ACE inhibitors during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible and irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to the ACE-inhibitor exposure.

These adverse effects do not appear to have resulted from intrauterine ACE-inhibitor exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to ACE inhibitors only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should make every effort to discontinue the use of ALTACE as soon as possible.

Rarely (probably less often than once in every thousand pregnancies), no alternative to ACE inhibitors will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examination should be performed to assess the intra-amniotic environment.

If oligohydramnios is observed, ALTACE should be discontinued unless it is considered lifesaving for the mother. Contraction stress testing (CST), a non-stress test (NST), or biophysical profiling (BPP) may be appropriate depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not be apparent until after the fetus has sustained irreversible injury.

Infants with histories of *in utero* exposure to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function. ALTACE, which crosses the placenta, can be removed from the neonatal circulation by these means, but limited experience has not shown that such removal is central to the treatment of these infants.

No teratogenic effects of ALTACE were seen in studies of pregnant rats, rabbits, and cynomolgus monkeys. On a mg/kg basis, the doses used were up to 2,500 times (in rats), 6.25 times (in rabbits), and 1,250 times (in monkeys) the maximum recommended human dose.

PRECAUTIONS: ***General:*** *Impaired Renal Function.* As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe congestive heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with angiotensin converting enzyme inhibitors, including ALTACE, may be associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death. In hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine may occur. Experience with another angiotensin converting enzyme inhibitor suggests that these increases are usually reversible upon discontinuation of ALTACE and/or diuretic therapy. In such patients renal function should be monitored during the first few weeks of therapy. Some hypertensive patients with no apparent pre-existing renal vascular disease have developed increases in blood urea nitrogen and serum creatinine, usually minor and transient, especially when ALTACE has been given concomitantly with a diuretic. This is more likely to occur in patients with pre-existing renal impairment. Dosage reduction of ALTACE and/or discontinuation of the diuretic may be required.

Evaluation of the hypertensive patient should always include assessment of renal function.

Hyperkalemia. In clinical trials, hyperkalemia (serum potassium greater than 5.7 mEq/L) occurred in approximately 1% of hypertensive patients receiving ALTACE. In most cases, these were isolated values, which resolved despite continued therapy. None of these patients was discontinued from the trials because of hyperkalemia. Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with ALTACE. (See DRUG INTERACTIONS.)

Cough: Cough has been reported with the use of ACE inhibitors. Characteristically, the cough is nonproductive, persistent and resolves after discontinuation of therapy. ACE inhibitor-induced cough should be considered as part of the differential diagnosis of cough.

Impaired Liver Function. Since ramipril is primarily metabolized by hepatic esterases to its active moiety, ramiprilat, patients with impaired liver function could develop markedly elevated plasma levels of ramipril. No formal pharmacokinetic studies have been carried out in hypertensive patients with impaired liver function.

Surgery/Anesthesia: In patients undergoing surgery or during anesthesia with agents that produce hypotension, ramipril may block angiotensin II formation that would otherwise occur secondary to compensatory renin release. Hypotension that occurs as a result of this mechanism can be corrected by volume expansion.

Information for Patients: *Angioedema:* Angioedema, including laryngeal edema, can occur with treatment with ACE inhibitors, especially following the first dose. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, eyes, lips, tongue, or difficulty in breathing) and to take no more drug until they have consulted with the prescribing physician.

Symptomatic Hypotension: Patients should be cautioned that lightheadedness can occur, especially during the first days of therapy, and it should be reported. Patients should be told that if syncope occurs, ALTACE™ (ramipril) should be discontinued until the physician has been consulted.

All patients should be cautioned that inadequate fluid intake or excessive perspiration, diarrhea, or vomiting can lead to an excessive fall in blood pressure, with the same consequences of lightheadedness and possible syncope.

Hyperkalemia: Patients should be told not to use salt substitutes containing potassium without consulting their physician.

Neutropenia: Patients should be told to promptly report any indication of infection (e.g., sore throat, fever), which could be a sign of neutropenia.

Pregnancy: Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to ACE inhibitors, and they should also be told that these consequences do not appear to have resulted from intrauterine ACE-inhibitor exposure that has been limited to the first trimester. These patients should also be asked to report pregnancies to their physicians as soon as possible.

Drug Interactions: *With Diuretics:* Patients on diuretics, especially those in whom diuretic therapy was recently instituted, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with ALTACE. The possibility of hypotensive effects with ALTACE can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with ALTACE. If this is not possible, the starting dose should be reduced.

With Potassium Supplements and Potassium-Sparing Diuretics: ALTACE can attenuate potassium loss caused by thiazide diuretics. Potassium-sparing diuretics (spironolactone, amiloride, triamterene, and others) or potassium supplements can increase the risk of hyperkalemia. Therefore, if concomitant use of such agents is indicated, they should be given with caution, and the patient's serum potassium should be monitored frequently.

With Lithium: Increased serum lithium levels and symptoms of lithium toxicity have been reported in patients receiving ACE inhibitors during therapy with lithium. These drugs should be coadministered with caution, and frequent monitoring of serum lithium levels is recommended. If a diuretic is also used, the risk of lithium toxicity may be increased.

Other: Neither ALTACE nor its metabolites have been found to interact with food, digoxin, or antacid.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No evidence of a tumorigenic effect was found when ramipril was given by gavage to rats (up to 500 mg/kg/day for 24 months) or to mice (up to 1,000 mg/kg/day for 18 months). Dosages greatly in excess of those recommended for humans produced hypertrophy of the renal juxtaglomerular apparatus in mice, rats, dogs, and monkeys. No mutagenic activity was detected in the Ames test in bacteria, the micronucleus test in mice, unscheduled DNA synthesis in a human cell line, or a forward gene-mutation assay in a Chinese hamster ovary cell line. Several metabolites and degradation products of ramipril were also negative in the Ames test. A study in rats with dosages as great as 500 mg/kg/day did not produce adverse effects on fertility.

Pregnancy: **Pregnancy Categories C (first trimester) and D (second and third trimesters): See WARNINGS: Fetal/neonatal morbidity and mortality.**

Nursing Mothers: Ingestion of a single 10 mg oral dose of ALTACE resulted in undetectable amounts of ramipril and its metabolites in breast milk. However, because multiple doses may produce low milk concentrations that are not predictable from single doses, ALTACE should not be administered to nursing mothers.

Geriatric Use: Of the total number of patients who received ramipril in US clinical studies of ALTACE, 11.0% were 65 and over while 0.2% were 75 and over. No overall differences in effectiveness or safety were observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

One pharmacokinetic study conducted in hospitalized elderly patients indicated that peak ramiprilat levels and area under the plasma concentration-time curve (AUC) for ramiprilat are higher in older patients.

Pediatric Use: Safety and effectiveness in children has not been established.

ADVERSE REACTIONS: ALTACE has been evaluated for safety in over 4,000 patients with hypertension; of these, 1,230 patients were studied in US controlled trials, and 1,107 were studied in foreign controlled trials. Almost 700 of these patients were treated for at least one year. The overall incidence of reported adverse events was similar in ALTACE and placebo patients. The most frequent clinical side effects (possibly or probably related to study drug) reported by patients receiving ALTACE in US placebo-controlled trials were: headache (5.4%), "dizziness" (2.2%) and fatigue or asthenia (2.0%), but only the last was more common in ALTACE patients than in patients given placebo. Generally, the side effects were mild and transient, and there was no relation to total dosage within the range of 1.25 to 20 mg. Discontinuation of therapy because of a side effect was required in approximately 3% of US patients treated with ALTACE. The most common reasons for discontinuation were: cough (1.0%), "dizziness" (0.5%), and impotence (0.4%).

The side effects considered possibly or probably related to study drug that occurred in US placebo-controlled trials in more than 1% of patients treated with ALTACE are shown below:

PATIENTS IN US PLACEBO-CONTROLLED STUDIES

	Altace (N = 651)		Placebo (N = 286)	
	n	%	n	%
Headache	35	5.4	17	5.9
"Dizziness"	14	2.2	9	3.1
Asthenia (Fatigue)	13	2.0	2	0.7
Nausea/Vomiting	7	1.1	3	1.0

In placebo-controlled trials, there was also an excess of upper respiratory infection and flu syndrome in the ramipril group. As these studies were carried out before the relationship of cough to ACE inhibitors was recognized, some of these events may represent ramipril-induced cough. In a later 1-year study, increased cough was seen in almost 12% of ramipril patients, with about 4% of these patients requiring discontinuation of treatment. Other adverse experiences reported in controlled clinical trials (in less than 1% of ramipril patients), or rarer events seen in postmarketing experience, include the following. (In some, a causal relationship to drug use is uncertain.)

Cardiovascular: Symptomatic hypotension (reported in 0.5% of patients in US trials) (see PRECAUTIONS and WARNINGS), syncope (not reported in US trials), angina pectoris, arrhythmia, chest pain, palpitations, myocardial infarction, and cerebrovascular events.

Renal: Some hypertensive patients with no apparent pre-existing renal disease have developed minor, usually transient, increases in blood urea nitrogen and serum creatinine when taking ALTACE, particularly when ALTACE was given concomitantly with a diuretic. (See WARNINGS.)

Angioneurotic Edema: Angioneurotic edema has been reported in 0.3% of patients in US clinical trials. (See WARNINGS.)

Cough: A tickling, dry, persistent, nonproductive cough has been reported with the use of ACE inhibitors. Approximately 1% of patients treated with ALTACE have required discontinuation because of cough. The cough disappears shortly after discontinuation of treatment. (See PRECAUTIONS.)

Gastrointestinal: Abdominal pain (sometimes with enzyme changes suggesting pancreatitis), anorexia, constipation, diarrhea, dry mouth, dyspepsia, dysphagia, gastroenteritis, nausea, increased salivation, taste disturbance, and vomiting.

Dermatologic: Apparent hypersensitivity reactions (manifested by dermatitis, pruritus, or rash, with or without fever), photosensitivity, and purpura.

Neurologic and Psychiatric: Anxiety, amnesia, convulsions, depression, hearing loss, insomnia, nervousness, neuralgia, neuropathy, paresthesia, somnolence, tinnitus, tremor, vertigo, and vision disturbances.

Fetal/Neonatal Morbidity and Mortality: See WARNINGS: Fetal/neonatal morbidity and mortality.

Other: arthralgia, arthritis, dyspnea, edema, epistaxis, impotence, increased sweating, malaise, myalgia, and weight gain.

Clinical Laboratory Test Findings: *Creatinine and Blood Urea Nitrogen:* Increases in creatinine levels occurred in 1.2% of patients receiving ALTACE alone, and in 1.5% of patients receiving ALTACE and a diuretic. Increases in blood urea nitrogen levels occurred in 0.5% of patients receiving ALTACE alone and in 3% of patients receiving ALTACE with a diuretic. None of these increases required discontinuation of treatment. Increases in these laboratory values are more likely to occur in patients with renal insufficiency or those pretreated with a diuretic and, based on experience with other ACE inhibitors, would be expected to be especially likely in patients with renal artery stenosis. (See PRECAUTIONS and WARNINGS.)

Since ramipril decreases aldosterone secretion, elevation of serum potassium can occur. Potassium supplements and potassium-sparing diuretics should be given with caution, and the patient's serum potassium should be monitored frequently. (See PRECAUTIONS and WARNINGS.)

Hemoglobin and Hematocrit: Decreases in hemoglobin or hematocrit (a low value and a decrease of 5 g/dl or 5% respectively) were rare, occurring in 0.4% of patients receiving ALTACE alone and in 1.5% of patients receiving ALTACE plus a diuretic. No US patients discontinued treatment because of decreases in hemoglobin or hematocrit.

Other (causal relationships unknown): Clinically important changes in standard laboratory tests were rarely associated with ALTACE administration. Elevations of liver enzymes, serum bilirubin, uric acid, and blood glucose have been reported, as have scattered incidents of leukopenia, eosinophilia, and proteinuria. In US trials, less than 0.2% of patients discontinued treatment for laboratory abnormalities; all of these were cases of proteinuria or abnormal liver-function tests.

OVERDOSAGE: Human overdoses of ramipril have not been reported, but the most common manifestation of human ramipril overdosage is likely to be hypotension. Because the hypotensive effect of ramipril is achieved through vasodilation and effective hypovolemia, it is reasonable to treat ramipril overdose by infusion of normal saline solution.

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*In some patients treated once daily, the antihypertensive effect may diminish toward the end of the dosing interval.

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ALL DAY ALL NIGHT

ALTACE™
ramipril

HOUR-TO-HOUR EFFICACY	24-hr blood pressure control with a once-daily dose*
DAY-TO-DAY ECONOMY	Priced lower than the four leading ACE inhibitors
YEAR-TO-YEAR COST CONTROL	No manufacturer's price increase through January 1, 2000

USE IN PREGNANCY When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, ALTACE should be discontinued as soon as possible See WARNINGS Fetal/neonatal morbidity and mortality

ALTACE is contraindicated in patients who are hypersensitive to this product and in patients with a history of angioedema related to previous treatment with an ACE inhibitor.

* In some patients treated once daily, the antihypertensive effect may diminish toward the end of the dosing interval.

Please see brief summary of prescribing information on the next page.

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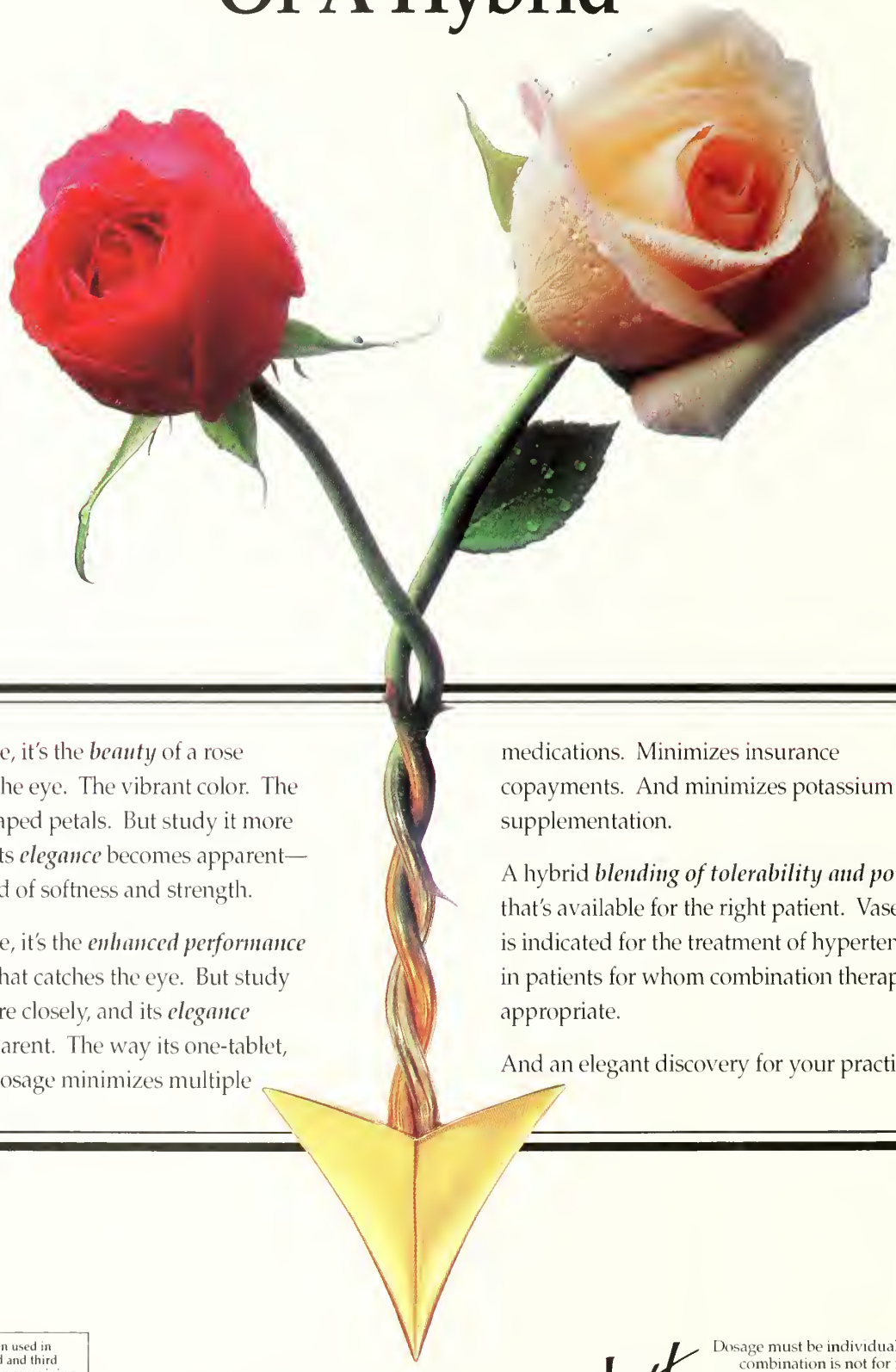
ETAL MEDICINE

Discover The Elegance Of A Hybrid



At first glance, it's the *beauty* of a rose that catches the eye. The vibrant color. The delicately shaped petals. But study it more closely, and its *elegance* becomes apparent—a gentle blend of softness and strength.

At first glance, it's the *enhanced performance* of Vaseretic that catches the eye. But study Vaseretic more closely, and its *elegance* becomes apparent. The way its one-tablet, once-a-day dosage minimizes multiple medications. Minimizes insurance copayments. And minimizes potassium supplementation.

A hybrid ***blending of tolerability and power*** that's available for the right patient. Vaseretic is indicated for the treatment of hypertension in patients for whom combination therapy is appropriate.

And an elegant discovery for your practice.

USE IN PREGNANCY: When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, Vaseretic® (Enalapril Maleate-Hydrochlorothiazide) should be discontinued as soon as possible. See WARNINGS, *Fetal/Neonatal Morbidity and Mortality.*

VASERETIC® 10-25
Enalapril Maleate-Hydrochlorothiazide

Next

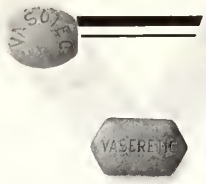
Dosage must be individualized; the fixed combination is not for initial therapy.

Evaluation of the hypertensive patient should always include assessment of renal function.

For a Brief Summary of Prescribing Information, see adjacent pages.

TABLETS
VASERETIC®
(ENALAPRIL MALEATE-HYDROCHLOROTHIAZIDE)

USE IN PREGNANCY: When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, VASERETIC® (Enalapril Maleate-Hydrochlorothiazide) should be discontinued as soon as possible. See WARNINGS, *Fetal/Neonatal Morbidity and Mortality.*



10 mg

25 mg

CONTRAINDICATIONS: VASERETIC is contraindicated in patients who are hypersensitive to any component of this product and in patients with a history of angioedema related to previous treatment with an angiotensin converting enzyme inhibitor. Because of the hydrochlorothiazide component, this product is contraindicated in patients with anuria or hypersensitivity to other sulfonamide-derived drugs.

WARNINGS: *General; Enalapril Maleate; Hypotension:* Excessive hypotension was rarely seen in uncomplicated hypertensive patients but is a possible consequence of enalapril use in severely salt/volume depleted persons such as those treated vigorously with diuretics or patients on dialysis.

Syncope has been reported in 1.3 percent of patients receiving VASERETIC. In patients receiving enalapril alone, the incidence of syncope is 0.5 percent. The overall incidence of syncope may be reduced by proper titration of the individual components. (See PRECAUTIONS, *Drug Interactions,* and ADVERSE REACTIONS.)

In patients with severe congestive heart failure, with or without associated renal insufficiency, excessive hypotension has been observed and may be associated with oliguria and/or progressive azotemia, and rarely with acute renal failure and/or death. Because of the potential fall in blood pressure in these patients, therapy should be started under very close medical supervision. Such patients should be followed closely for the first two weeks of treatment and whenever the dose of enalapril and/or diuretic is increased. Similar considerations may apply to patients with ischemic heart or cerebrovascular disease, in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident.

If hypotension occurs, the patient should be placed in the supine position and, if necessary, receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses, which usually can be given without difficulty once the blood pressure has increased after volume expansion.

Angioedema: Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported in patients treated with angiotensin converting enzyme inhibitors, including enalapril. In such cases VASERETIC should be promptly discontinued and appropriate therapy and monitoring should be provided until complete and sustained resolution of signs and symptoms has occurred. In instances where swelling has been confined to the face and lips the condition has generally resolved without treatment, although antihistamines have been useful in relieving symptoms. Angioedema associated with laryngeal edema may be fatal. **Where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, appropriate therapy, e.g., subcutaneous epinephrine solution 1:1000 (0.3 mL to 0.5 mL) and/or measures necessary to ensure a patent airway, should be promptly provided.** (See ADVERSE REACTIONS.)

Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor (see also CONTRAINDICATIONS).

Neutropenia/Agranulocytosis: Another angiotensin converting enzyme inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression, rarely in uncomplicated patients but more frequently in patients with renal impairment especially if they also have a collagen vascular disease. Available data from clinical trials of enalapril are insufficient to show that enalapril does not cause agranulocytosis at similar rates. Marketing experience has revealed several cases of neutropenia or agranulocytosis in which a causal relationship to enalapril cannot be excluded. Periodic monitoring of white blood cell counts in patients with collagen vascular disease and renal disease should be considered.

Hydrochlorothiazide: Thiazides should be used with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. Cumulative effects of the drug may develop in patients with impaired renal function.

Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.

Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma.

The possibility of exacerbation or activation of systemic lupus erythematosus has been reported.

Lithium generally should not be given with thiazides (see PRECAUTIONS, *Drug Interactions, Enalapril Maleate and Hydrochlorothiazide*).

Pregnancy; Enalapril-Hydrochlorothiazide: There was no teratogenicity in rats given up to 90 mg/kg/day of enalapril (150 times the maximum human dose) in combination with 10 mg/kg/day of hydrochlorothiazide (2 ½ times the maximum human dose) or in mice given up to 30 mg/kg/day of enalapril (50 times the maximum human dose) in combination with 10 mg/kg/day of hydrochlorothiazide (2 ½ times the maximum human dose). At these doses, fetotoxicity expressed as a decrease in average fetal weight occurred in both species. No fetotoxicity occurred at lower doses: 30/10 mg/kg/day of enalapril-hydrochlorothiazide in rats and 10/10 mg/kg/day of enalapril-hydrochlorothiazide in mice.

When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, VASERETIC should be discontinued as soon as possible. (See *Enalapril Maleate, Fetal/Neonatal Morbidity and Mortality,* below.)

Enalapril Maleate; Fetal/Neonatal Morbidity and Mortality: ACE inhibitors can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature. When pregnancy is detected, ACE inhibitors should be discontinued as soon as possible.

The use of ACE inhibitors during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to the ACE-inhibitor exposure.

These adverse effects do not appear to have resulted from intrauterine ACE-inhibitor exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to ACE inhibitors only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should make every effort to discontinue the use of VASERETIC as soon as possible.

Rarely (probably less often than once in every thousand pregnancies), no alternative to ACE inhibitors will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intraamniotic environment.

If oligohydramnios is observed, VASERETIC should be discontinued unless it is considered lifesaving for the mother. Contraction stress testing (CST), a non-stress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of *in utero* exposure to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function. Enalapril, which crosses the placenta, has been removed from neonatal circulation by peritoneal dialysis with some clinical benefit, and theoretically may be removed by exchange transfusion, although there is no experience with the latter procedure.

No teratogenic effects of enalapril were seen in studies of pregnant rats and rabbits. On a mg/kg basis, the doses used were up to 333 times (in rats), and 50 times (in rabbits) the maximum recommended human dose.

Hydrochlorothiazide; Teratogenic Effects: Reproduction studies in the rabbit, the mouse and the rat at doses up to 100 mg/kg/day (50 times the human dose) showed no evidence of external abnormalities of the fetus due to hydrochlorothiazide. Hydrochlorothiazide given in a two-litter study in rats at doses of 4 - 5.6 mg/kg/day (approximately 1 - 2 times the usual daily human dose) did not impair fertility or produce birth abnormalities in the offspring. Thiazides cross the placental barrier and appear in cord blood.

Nonteratogenic Effects: These may include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult.

PRECAUTIONS: *General; Enalapril Maleate, Impaired Renal Function:* As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe congestive heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with angiotensin converting enzyme inhibitors, including enalapril, may be associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death.

In clinical studies in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine were observed in 20 percent of patients. These increases were almost always reversible upon discontinuation of enalapril and/or diuretic therapy. In such patients renal function should be monitored during the first few weeks of therapy.

Some patients with hypertension or heart failure with no apparent preexisting renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when enalapril has been given concomitantly with a diuretic. This is more likely to occur in patients with pre-existing renal impairment. Dosage reduction of enalapril and/or discontinuation of the diuretic may be required.

Evaluation of the hypertensive patient should always include assessment of renal function.

Hemodialysis Patients: Anaphylactoid reactions have been reported in patients dialyzed with high-flux membranes (e.g., AN 69*) and treated concomitantly with an ACE inhibitor. In these patients consideration should be given to using a different type of dialysis membrane or a different class of antihypertensive agent.

Hyperkalemia: Elevated serum potassium (greater than 5.7 mEq/L) was observed in approximately one percent of hypertensive patients in clinical trials treated with enalapril alone. In most cases these were isolated values which resolved despite continued therapy, although hyperkalemia was a cause of discontinuation of therapy in 0.28 percent of hypertensive patients. Hyperkalemia was less frequent (approximately 0.1 percent) in patients treated with enalapril plus hydrochlorothiazide. Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with enalapril. (See *Drug Interactions.*)

Cough: Cough has been reported with the use of ACE inhibitors. Characteristically, the cough is nonproductive, persistent and resolves after discontinuation of therapy. ACE inhibitor-induced cough should be considered as part of the differential diagnosis of cough.

Surgery/Anesthesia: In patients undergoing major surgery or during anesthesia with agents that produce hypotension, enalapril may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Hydrochlorothiazide: Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals. All patients receiving thiazide therapy should be observed for clinical signs of fluid or electrolyte imbalance: hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Warning signs or symptoms of fluid and electrolyte imbalance, irrespective of cause, include dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, confusion, seizures, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting.

Hypokalemia may develop, especially with brisk diuresis, when severe cirrhosis is present, or after prolonged therapy. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Hypokalemia may cause cardiac arrhythmia and may also sensitize or exaggerate the response of the heart to the toxic effects of digitalis (e.g., increased ventricular irritability). Because enalapril reduces the production of aldosterone, concomitant therapy with enalapril attenuates the diuretic-induced potassium loss (see *Drug Interactions, Agents Increasing Serum Potassium*).

Although any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease), chloride replacement may be required in the treatment of metabolic alkalosis.

Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction, rather than administration of salt except in rare instances when the hyponatremia is life-threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Hyperuricemia may occur or frank gout may be precipitated in certain patients receiving thiazide therapy.

In diabetic patients dosage adjustments of insulin or oral hypoglycemic agents may be required. Hyperglycemia may occur with thiazide diuretics. Thus latent diabetes mellitus may become manifest during thiazide therapy.

The antihypertensive effects of the drug may be enhanced in the postsympathectomy patient.

If progressive renal impairment becomes evident consider withholding or discontinuing diuretic therapy.

Thiazides have been shown to increase the urinary excretion of magnesium; this may result in hypomagnesemia.

Thiazides may decrease urinary calcium excretion. Thiazides may cause intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

Increases in cholesterol and triglyceride levels may be associated with thiazide diuretic therapy.

Information for Patients; Angioedema: Angioedema, including laryngeal edema, may occur especially following the first dose of enalapril. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, extremities, eyes, lips, tongue, difficulty in swallowing or breathing) and to take no more drug until they have consulted with the prescribing physician.

Hypotension: Patients should be cautioned to report lightheadedness especially during the first few days of therapy. If actual syncope occurs, the patients should be told to discontinue the drug until they have consulted with the prescribing physician.

All patients should be cautioned that excessive perspiration and dehydration may lead to an excessive fall in blood pressure because of reduction in fluid volume. Other causes of volume depletion such as vomiting or diarrhea may also lead to a fall in blood pressure; patients should be advised to consult with the physician.

Hyperkalemia: Patients should be told not to use salt substitutes containing potassium without consulting their physician.

Neutropenia: Patients should be told to report promptly any indication of infection (e.g., sore throat, fever) which may be a sign of neutropenia.

Pregnancy: Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to ACE inhibitors, and they should also be told that these consequences do not appear to have resulted from intrauterine ACE-inhibitor exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.

NOTE: As with many other drugs, certain advice to patients being treated with VASERETIC is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Drug Interactions; Enalapril Maleate, Hypotension—Patients on Diuretic Therapy: Patients on diuretics and especially those in whom diuretic therapy was recently instituted, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with enalapril. The possibility of hypotensive effects with enalapril can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with enalapril. If it is necessary to continue the diuretic, provide medical supervision for at least two hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS.)

Agents Causing Renin Release: The antihypertensive effect of enalapril is augmented by antihypertensive agents that cause renin release (e.g., diuretics).

Other Cardiovascular Agents: Enalapril has been used concomitantly with beta adrenergic-blocking agents, methyldopa, nitrates, calcium-blocking agents, hydralazine and prazosin without evidence of clinically significant adverse interactions.

Agents Increasing Serum Potassium: Enalapril attenuates diuretic-induced potassium loss. Potassium-sparing diuretics (e.g., spironolactone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium. Therefore, if concomitant use of these agents is indicated because of demonstrated hypokalemia they should be used with caution and with frequent monitoring of serum potassium.

Lithium: Lithium toxicity has been reported in patients receiving lithium concomitantly with drugs which cause elimination of sodium, including ACE inhibitors. A few cases of lithium toxicity have been reported in patients receiving concomitant enalapril and lithium and were reversible upon discontinuation of both drugs. It is recommended that serum lithium levels be monitored frequently if enalapril is administered concomitantly with lithium.

Hydrochlorothiazide: When administered concurrently the following drugs may interact with thiazide diuretics:

Alcohol, barbiturates, or narcotics—potentiation of orthostatic hypotension may occur.

Antidiabetic drugs (oral agents and insulin)—dosage adjustment of the antidiabetic drug may be required.

Other antihypertensive drugs—additive effect or potentiation.

Cholestyramine and colestipol resins—Cholestyramine and colestipol resins bind the hydrochlorothiazide and reduce its absorption from the gastrointestinal tract by up to 85 and 43 percent, respectively. Thiazides may be administered two to four hours before the resin when the two drugs are used concomitantly.

Corticosteroids, ACTH—intensified electrolyte depletion, particularly hypokalemia.

Pressor amines (e.g., norepinephrine)—possible decreased response to pressor amines but not sufficient to preclude their use.

Skeletal muscle relaxants, nondepolarizing (e.g., tubocurarine)—possible increased responsiveness to the muscle relaxant.

Lithium—should not generally be given with diuretics. Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity. Refer to the package insert for lithium preparations before use of such preparations with VASERETIC.

Non-steroidal Anti-inflammatory Drugs—In some patients, the administration of a non-steroidal anti-inflammatory agent can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing and thiazide diuretics. Therefore, when VASERETIC and non-steroidal anti-inflammatory agents are used concomitantly, the patient should be observed closely to determine if the desired effect of the diuretic is obtained.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Enalapril in combination with hydrochlorothiazide was not mutagenic in the Ames microbial mutagen test with or without metabolic activation. Enalapril-hydrochlorothiazide did not produce DNA single strand breaks in an *in vitro* alkaline elution assay in rat hepatocytes or chromosomal aberrations in an *in vivo* mouse

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bone marrow assay.

Enalapril Maleate: There was no evidence of a tumorigenic effect when enalapril was administered for 106 weeks to rats at doses up to 90 mg/kg/day (150 times* the maximum daily human dose). Enalapril has also been administered for 94 weeks to male and female mice at doses up to 90 and 180 mg/kg/day, respectively, (150 and 300 times* the maximum daily dose for humans) and showed no evidence of carcinogenicity.

Neither enalapril maleate nor the active diacid was mutagenic in the Ames microbial mutagen test with or without metabolic activation. Enalapril was also negative in the following genotoxicity studies: rec-assay, reverse mutation assay with *E. coli*, sister chromatid exchange with cultured mammalian cells, and the micronucleus test with mice, as well as in an *in vivo* cytogenic study using mouse bone marrow.

There were no adverse effects on reproductive performance in male and female rats treated with 10 to 90 mg/kg/day of enalapril.

Hydrochlorothiazide: Two-year feeding studies in mice and rats conducted under the auspices of the National Toxicology Program (NTP) uncovered no evidence of a carcinogenic potential of hydrochlorothiazide in female mice (at doses of up to approximately 600 mg/kg/day) or in male and female rats (at doses of up to approximately 100 mg/kg/day). The NTP, however, found equivocal evidence for hepatocarcinogenicity in male mice.

Hydrochlorothiazide was not genotoxic *in vitro* in the Ames mutagenicity assay of *Salmonella typhimurium* strains TA 98, TA 100, TA 1535, TA 1537, and TA 1538 and in the Chinese Hamster Ovary (CHO) test for chromosomal aberrations, or *in vivo* in assays using mouse germinal cell chromosomes, Chinese hamster bone marrow chromosomes, and the *Drosophila* sex-linked recessive lethal trait gene. Positive test results were obtained only in the *in vitro* CHO Sister Chromatid Exchange (clastogenicity) and in the Mouse Lymphoma Cell (mutagenicity) assays, using concentrations of hydrochlorothiazide from 43 to 1300 µg/mL, and in the *Aspergillus nidulans* non-disjunction assay at an unspecified concentration.

Hydrochlorothiazide had no adverse effects on the fertility of mice and rats of either sex in studies wherein these species were exposed, via their diet, to doses of up to 100 and 4 mg/kg, respectively, prior to conception and throughout gestation.

Pregnancy, Pregnancy Categories C (first trimester) *and D* (second and third trimesters). See WARNINGS, *Pregnancy, Enalapril Maleate, Fetal/Neonatal Morbidity and Mortality.*

Nursing Mothers: Enalapril and enalaprilat are detected in human milk in trace amounts. Thiazides do appear in human milk. Because of the potential for serious reactions in nursing infants from either drug, a decision should be made whether to discontinue nursing or to discontinue VASERETIC, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: VASERETIC has been evaluated for safety in more than 1500 patients, including over 300 patients treated for one year or more. In clinical trials with VASERETIC no adverse experiences peculiar to this combination drug have been observed. Adverse experiences that have occurred, have been limited to those that have been previously reported with enalapril or hydrochlorothiazide.

The most frequent clinical adverse experiences in controlled trials were: dizziness (8.6 percent), headache (5.5 percent), fatigue (3.9 percent) and cough (3.5 percent). Adverse experiences occurring in greater than two percent of patients treated with VASERETIC in controlled clinical trials were: muscle cramps (2.7 percent), nausea (2.5 percent), asthenia (2.4 percent), orthostatic effects (2.3 percent), impotence (2.2 percent), and diarrhea (2.1 percent).

Clinical adverse experiences occurring in 0.5 to 2.0 percent of patients in controlled trials included: *Body As A Whole:* Syncope, chest pain, abdominal pain, *Cardiovascular:* Orthostatic hypotension, palpitation, tachycardia, *Digestive:* Vomiting, dyspepsia, constipation, flatulence, dry mouth; *Nervous/Psychiatric:* Insomnia, nervousness, paresthesia, somnolence, vertigo, *Skin:* Pruritus, rash, *Other:* Dyspnea, gout, back pain, arthralgia, diaphoresis, decreased libido, tinnitus, urinary tract infection.

Angioedema: Angioedema has been reported in patients receiving VASERETIC (0.6 percent). Angioedema associated with laryngeal edema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis and/or larynx occurs, treatment with VASERETIC should be discontinued and appropriate therapy instituted immediately. (See WARNINGS.)

Hypotension: In clinical trials, adverse effects relating to hypotension occurred as follows: hypotension (0.9 percent), orthostatic hypotension (1.5 percent), other orthostatic effects (2.3 percent). In addition syncope occurred in 1.3 percent of patients. (See WARNINGS.)

Cough: See PRECAUTIONS, *Cough.*

Clinical Laboratory Test Findings, Serum Electrolytes: See PRECAUTIONS.

Creatinine, Blood Urea Nitrogen: In controlled clinical trials minor increases in blood urea nitrogen and serum creatinine, reversible upon discontinuation of therapy, were observed in about 0.6 percent of patients with essential hypertension treated with VASERETIC. More marked increases have been reported in other enalapril experience. Increases are more likely to occur in patients with renal artery stenosis. (See PRECAUTIONS.)

Serum Uric Acid, Glucose, Magnesium, and Calcium: See PRECAUTIONS.

Hemoglobin and Hematocrit: Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.3 g percent and 1.0 vol percent, respectively) occur frequently in hypertensive patients treated with VASERETIC but are rarely of clinical importance unless another cause of anemia coexists. In clinical trials, less than 0.1 percent of patients discontinued therapy due to anemia.

Liver Function Tests: Rarely, elevations of liver enzymes and/or serum bilirubin have occurred.

Other adverse reactions that have been reported with the individual components are listed below and, within each category, are in order of decreasing severity.

Enalapril Maleate—Enalapril has been evaluated for safety in more than 10,000 patients. In clinical trials adverse reactions which occurred with enalapril were also seen with VASERETIC. However, since enalapril has been marketed, the following adverse reactions have been reported: *Body As A Whole:* Anaphylactoid reactions (see PRECAUTIONS, *Hemodialysis Patients*); *Cardiovascular:* Cardiac arrest, myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high risk patients (see WARNINGS, *Hypotension*); pulmonary embolism and infarction, pulmonary edema; rhythm disturbances including atrial tachycardia and bradycardia; atrial fibrillation, hypotension, angina pectoris; *Digestive:* Ileus, pancreatitis, hepatic failure, hepatitis (hepatocellular [proven on rechallenge] or cholestatic jaundice), melena, anorexia, glossitis, stomatitis, dry mouth; *Hematologic:* Rare cases of neutropenia, thrombocytopenia and bone marrow depression, a few cases of hemolysis in patients with G-6-PD deficiency have been reported in which a causal relationship to enalapril cannot be excluded; *Nervous System/Psychiatric:* Depression, confusion, ataxia, peripheral neuropathy (e.g., paresthesia, dysesthesia); *Urogenital:* Renal failure, oliguria, renal dysfunction (see PRECAUTIONS), flank pain, gynecomastia; *Respiratory:* Pulmonary infiltrates, bronchospasm, pneumonia, bronchitis, rhinorrhea, sore throat and hoarseness, asthma, upper respiratory infection; *Skin:* Exfoliative dermatitis, toxic epidermal necrolysis, Stevens-Johnson syndrome, herpes zoster, erythema multiforme, urticaria, alopecia, flushing, photosensitivity; *Special Senses:* Blurred vision, taste alteration, anosmia, conjunctivitis, dry eyes, tearing.

Miscellaneous: A symptom complex has been reported which may include a positive ANA, an elevated erythrocyte sedimentation rate, arthralgia/arthritis, myalgia, fever, serositis, vasculitis, leukocytosis, eosinophilia, photosensitivity, rash and other dermatologic manifestations.

Fetal/Neonatal Morbidity and Mortality: See WARNINGS, *Pregnancy, Enalapril Maleate, Fetal/Neonatal Morbidity and Mortality.*

Hydrochlorothiazide—Body as a Whole: Weakness; *Digestive:* Pancreatitis, jaundice (intrahepatic cholestatic jaundice), sialadenitis, cramping, gastric irritation, anorexia; *Hematologic:* Aplastic anemia, agranulocytosis, leukopenia, hemolytic anemia, thrombocytopenia; *Hypersensitivity:* Purpura, photosensitivity, urticaria, necrotizing angiitis (vasculitis and cutaneous vasculitis), fever, respiratory distress including pneumonitis and pulmonary edema, anaphylactic reactions; *Musculoskeletal:* Muscle spasm; *Nervous System/Psychiatric:* Restlessness; *Renal:* Renal failure, renal dysfunction, interstitial nephritis (see WARNINGS); *Skin:* Erythema multiforme including Stevens-Johnson syndrome, exfoliative dermatitis including toxic epidermal necrolysis, alopecia; *Special Senses:* Transient blurred vision, xanthopsia.

* Based on patient weight of 50 kg.

For more detailed information, consult your DuPont Pharma Representative or see Prescribing Information.

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YOCON®
YOHIMBINE HCl

Description: Yohimbine is a 3a-15a-20B-17a-hydroxy Yohimbine-16a-carboxylic acid methyl ester. The alkaloid is found in Rubaceae and related trees. Also in Rauwolfia Serpentina (L) Benth. Yohimbine is an indolalkylamine alkaloid with chemical similarity to reserpine. It is a crystalline powder, odorless. Each compressed tablet contains (1/12 gr.) 5.4 mg of Yohimbine Hydrochloride.

Action: Yohimbine blocks presynaptic alpha-2 adrenergic receptors. Its action on peripheral blood vessels resembles that of reserpine, though it is weaker and of short duration. Yohimbine's peripheral autonomic nervous system effect is to increase parasympathetic (cholinergic) and decrease sympathetic (adrenergic) activity. It is to be noted that in male sexual performance, erection is linked to cholinergic activity and to alpha-2 adrenergic blockade which may theoretically result in increased penile inflow, decreased penile outflow or both.

Yohimbine exerts a stimulating action on the mood and may increase anxiety. Such actions have not been adequately studied or related to dosage although they appear to require high doses of the drug. Yohimbine has a mild anti-diuretic action, probably via stimulation of hypothalmic centers and release of posterior pituitary hormone.

Reportedly, Yohimbine exerts no significant influence on cardiac stimulation and other effects mediated by B-adrenergic receptors, its effect on blood pressure, if any, would be to lower it; however no adequate studies are at hand to quantitate this effect in terms of Yohimbine dosage.

Indications: Yocon® is indicated as a sympathicolytic and mydriatic. It may have activity as an aphrodisiac.

Contraindications: Renal diseases, and patient's sensitive to the drug. In view of the limited and inadequate information at hand, no precise tabulation can be offered of additional contraindications.

Warning: Generally, this drug is not proposed for use in females and certainly must not be used during pregnancy. Neither is this drug proposed for use in pediatric, geriatric or cardio-renal patients with gastric or duodenal ulcer history. Nor should it be used in conjunction with mood-modifying drugs such as antidepressants, or in psychiatric patients in general.

Adverse Reactions: Yohimbine readily penetrates the (CNS) and produces a complex pattern of responses in lower doses than required to produce peripheral a-adrenergic blockade. These include, anti-diuresis, a general picture of central excitation including elevation of blood pressure and heart rate, increased motor activity, irritability and tremor. Sweating, nausea and vomiting are common after parenteral administration of the drug.[1,2] Also dizziness, headache, skin flushing reported when used orally.[1,3]

Dosage and Administration: Experimental dosage reported in treatment of erectile impotence.[1,3,4] 1 tablet (5.4 mg) 3 times a day, to adult males taken orally. Occasional side effects reported with this dosage are nausea, dizziness or nervousness. In the event of side effects dosage to be reduced to ½ tablet 3 times a day, followed by gradual increases to 1 tablet 3 times a day. Reported therapy not more than 10 weeks.[3]

How Supplied: Oral tablets of YOCON® 1/12 gr. 5.4mg in bottles of 100's NDC 53159-001-01, 1000's NDC 53159-001-10 and Blister-Paks of 30's NDC 53159-001-30

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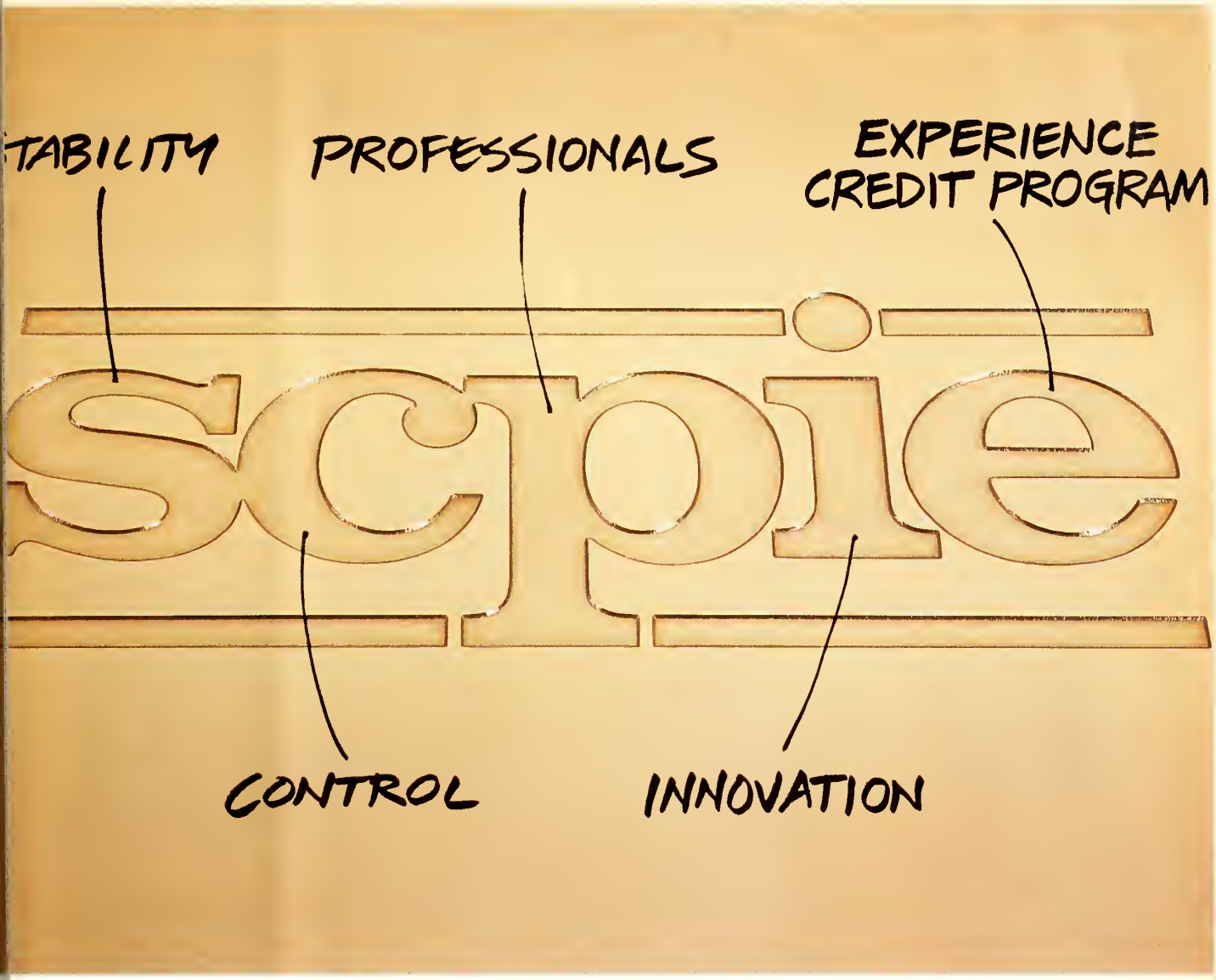

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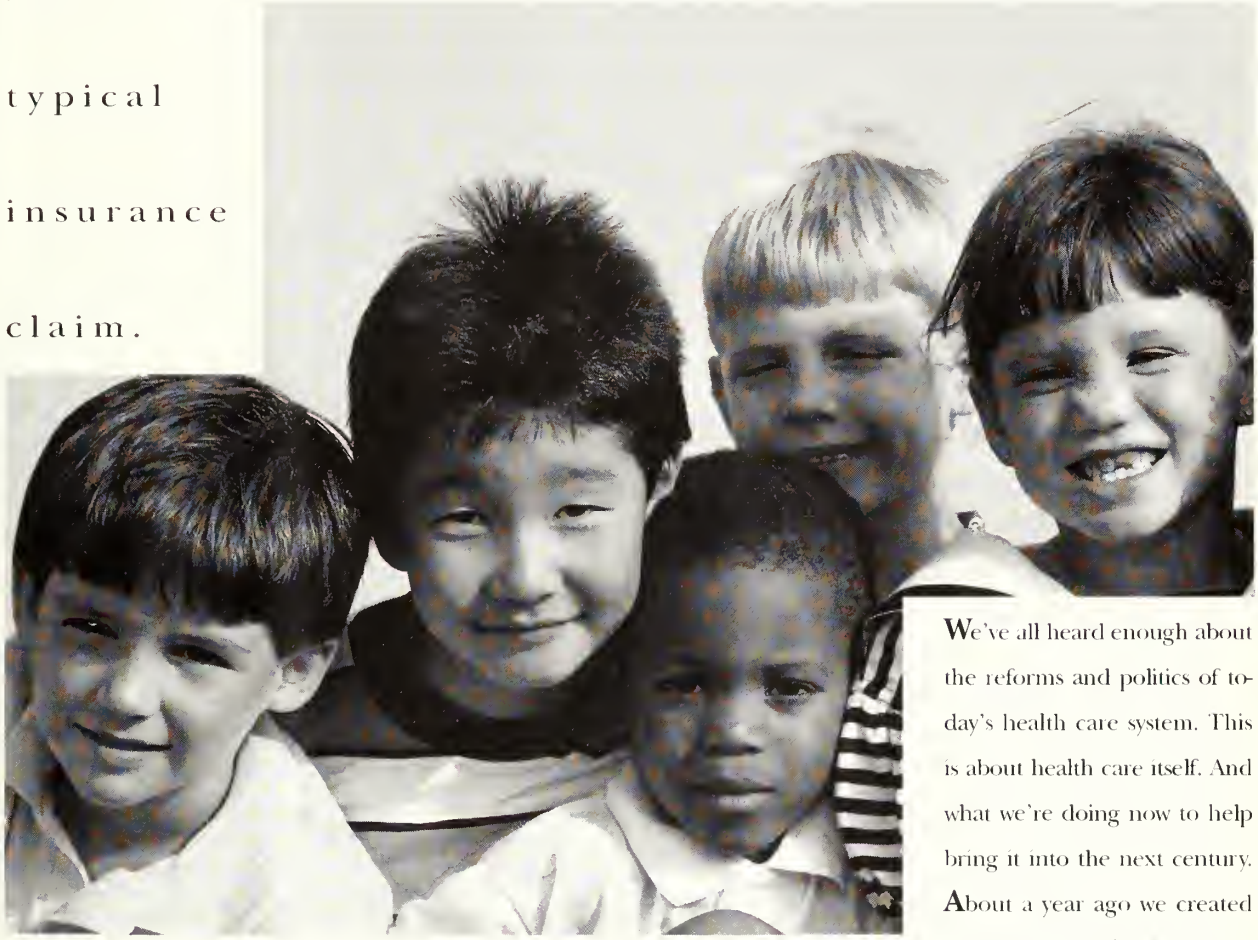

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BRIEF SUMMARY

Contraindications: Severe LV dysfunction (see *Warnings*), hypotension (systolic pressure < 90 mm Hg) or cardiogenic shock, sick sinus syndrome (if no pacemaker is present), 2nd- or 3rd-degree AV block (if no pacemaker is present), atrial flutter/fibrillation with an accessory bypass tract (eg, WPW or LGL syndromes), hypersensitivity to verapamil.

Warnings: Verapamil should be avoided in patients with severe LV dysfunction (eg, ejection fraction < 30%) or moderate to severe symptoms of cardiac failure and in patients with any degree of ventricular dysfunction if they are receiving a beta-blocker. Control milder heart failure with optimum digitalization and/or diuretics before Calan SR is used. Verapamil may occasionally produce hypotension. Elevations of liver enzymes have been reported. Several cases have been demonstrated to be produced by verapamil. Periodic monitoring of liver function in patients on verapamil is prudent. Some patients with paroxysmal and/or chronic atrial flutter/fibrillation and an accessory AV pathway (eg, WPW or LGL syndromes) have developed an increased antegrade conduction across the accessory pathway bypassing the AV node, producing a very rapid ventricular response or ventricular fibrillation after receiving I.V. verapamil (or digitalis). Because of this risk, oral verapamil is contraindicated in such patients. AV block may occur (2nd- and 3rd-degree, 0.8%). Development of marked 1st-degree block or progression to 2nd- or 3rd-degree block requires reduction in dosage or, rarely, discontinuation and institution of appropriate therapy. Sinus bradycardia, 2nd-degree AV block, sinus arrest, pulmonary edema and/or severe hypotension were seen in some critically ill patients with hypertrophic cardiomyopathy who were treated with verapamil.

Precautions: Verapamil should be given cautiously to patients with impaired hepatic function (in severe dysfunction use about 30% of the normal dose) or impaired renal function, and patients should be monitored for abnormal prolongation of the PR interval or other signs of overdosage. Verapamil may decrease neuromuscular transmission in patients with Duchenne's muscular dystrophy and may prolong recovery from the neuromuscular blocking agent vecuronium. It may be necessary to decrease verapamil dosage in patients with attenuated neuromuscular transmission. Combined therapy with beta-adrenergic blockers and verapamil may result in additive negative effects on heart rate, atrioventricular conduction and/or cardiac contractility; there have been reports of excessive bradycardia and AV block, including complete heart block. The risks of such combined therapy may outweigh the benefits. The combination should be used only with caution and close monitoring. Decreased metoprolol and propranolol clearance may occur when either drug is administered concomitantly with verapamil. A variable effect has been seen with combined use of atenolol. Chronic verapamil treatment can increase serum digoxin levels by 50% to 75% during the first week of therapy, which can result in digitalis toxicity. In patients with hepatic cirrhosis, verapamil may reduce total body clearance and extrarenal clearance of digitoxin. The digoxin dose should be reduced when verapamil is given, and the patient carefully monitored. Verapamil will usually have an additive effect in patients receiving blood-pressure-lowering agents. Disopyramide should not be given within 48 hours before or 24 hours after verapamil administration. Concomitant use of flecainide and verapamil may have additive effects on myocardial contractility, AV conduction, and repolarization. Combined verapamil and quinidine therapy in patients with hypertrophic cardiomyopathy should be avoided, since significant hypotension may result. Concomitant use of lithium and verapamil may result in an increased sensitivity to lithium (neurotoxicity), with either no change or an increase in serum lithium levels; however, it may also result in a lowering of serum lithium levels. Patients receiving both drugs must be monitored carefully. Verapamil may increase carbamazepine concentrations during combined use. Rifampin may reduce verapamil bioavailability. Phenobarbital may increase verapamil clearance. Verapamil may increase serum levels of cyclosporin. Verapamil may inhibit the clearance and increase the plasma levels of theophylline. Concomitant use of inhalation anesthetics and calcium antagonists needs careful titration to avoid excessive cardiovascular depression. Verapamil may potentiate the activity of neuromuscular blocking agents (curare-like and depolarizing); dosage reduction may be required. There was no evidence of a carcinogenic potential of verapamil administered to rats for 2 years. A study in rats did not suggest a tumorigenic potential, and verapamil was not mutagenic in the Ames test. Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy, labor, and delivery only if clearly needed. Verapamil is excreted in breast milk; therefore, nursing should be discontinued during verapamil use.

Adverse Reactions: Constipation (7.3%), dizziness (3.3%), nausea (2.7%), hypotension (2.5%), headache (2.2%), edema (1.9%), CHF, pulmonary edema (1.8%), fatigue (1.7%), dyspnea (1.4%), bradycardia: HR < 50/min (1.4%), AV block: total 1°,2°,3° (1.2%), 2° and 3° (0.8%), rash (1.2%), flushing (0.6%), elevated liver enzymes, reversible non-obstructive paralytic ileus. The following reactions, reported in 1.0% or less of patients, occurred under conditions where a causal relationship is uncertain: angina pectoris, atrioventricular dissociation, chest pain, claudication, myocardial infarction, palpitations, purpura (vasculitis), syncope, diarrhea, dry mouth, gastrointestinal distress, gingival hyperplasia, ecchymosis or bruising, cerebrovascular accident, confusion, equilibrium disorders, insomnia, muscle cramps, paresthesia, psychotic symptoms, shakiness, somnolence, arthralgia and rash, exanthema, hair loss, hyperkeratosis, macules, sweating, urticaria, Stevens-Johnson syndrome, erythema multiforme, blurred vision, gynecomastia, galactorrhea/hyperprolactinemia, increased urination, spotty menstruation, impotence.

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ANESTHESIOLOGY

October 17-23—**Hawaiian Seminar on Clinical Anesthesia.** California Society of Anesthesiologists at Four Seasons Hotel, Wailea, Maui, Hawaii. Sun-Sat. 23 hrs. $425. Contact: CSA, 1065 E Hillsdale Blvd, Ste 410, Foster City 94404. (800) 345-3691.

November 12-14—**Anesthesiology Update: 1993.** UCD at Monterey Plaza. Fri-Sun. 14 hrs. $275-$375. Contact: UCD.

November 19-20—**3rd Annual Pain Management.** UCD at Silverado Country Club, Napa. Fri-Sat. Contact: UCD.

January 16-22—**Hawaiian Seminar on Clinical Anesthesia.** California Society of Anesthesiologists at Westin Maui, Kaanapali Beach. Sun-Sat. 21 hrs. $425. Contact: CSA, 1065 E Hillsdale Blvd, Ste 410, Foster City 94404. (800) 345-3691.

January 28-30—**32nd Clinical Conference in Pediatric Anesthesiology.** Children's Hospital Los Angeles at Disneyland Hotel, Anaheim. Fri-Sun. 15 hrs. Contact: Children's Hospital, PO Box 54700, Los Angeles 90054. (213) 669-2262.

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November 8-12—**Emergency Medicine Symposium III.** UCSD at San Diego Hilton. Mon-Fri. 32 hrs. $495. Contact: UCSD.

December 5-10—**14th Annual Conference: Current Concepts in Emergency Care.** American College of Emergency Physicians Washington Chapter at Maui Intercontinental Resort, Maui, Hawaii. Sun-Fri. 20 hrs. Contact: Kailani World Travel, 4192 Meridian Ave, Box 9751, Bellingham, WA 98227. (800) 544-9269 or (206) 671-1800.

January 10-14—**Emergency Medicine Symposia I.** UCSD at La Jolla Marriott. Mon-Fri. 32 hrs. $495. Contact: UCSD.

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18th Annual Internal Medicine Series
• March 20-26, 1994 •
The Hilton, Walt Disney World Village

18th Annual Infectious Disease & Antibiotic Therapy Conference
• March 30-April 1, 1994 •
The Hilton, Walt Disney World Village

17th Annual Critical Care Medicine Conference
• April 6-9, 1994 •
The Hilton, Walt Disney World Village

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CONTINUING MEDICAL EDUCATION

(Continued from Page 242)

October 30—**Selected Topics in Cardiology: A Course for Primary Care Physicians.** UCLA at Miramar Sheraton Hotel, Santa Monica. Sat. 5 hrs. $40. Contact: UCLA Extension.

November 10-13—**North American Primary Care Research Group—Research Frontiers in Primary Care and Prevention.** UCSD at Hyatt Islandia on Mission Bay, San Diego. Wed-Sat. 23 hrs. $400. Contact: UCSD.

December 2-4—**Obstetrics and Gynecology Conference.** University of Nebraska at Bally's Las Vegas. Thurs-Sat. $275. Contact: University of Nebraska Medical Center, 600 S 42nd St, Omaha, NE 68198-5651. (402) 559-4152 or (800) 642-1095.

January 21-23—**Practical Dermatology and Dermatologic Office Procedures for the Primary Care Physician.** UCSD at Hyatt Regency, La Jolla. Fri-Sun. 20 hrs. $495. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

February 18-20—**Office Gynecology for the Primary Care Physician.** SDSU at Hyatt Islandia, San Diego. Fri-Sun. 20 hrs. $450. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

GERIATRICS

November 8-10—**Geriatrics Update: 1993.** Sharp Memorial Hospital at Loew's Coronado Bay Resort, San Diego. Mon-Wed. 20 hrs. $425. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

INFECTIOUS DISEASES

November 5-7—**Advances in Infectious Disease.** Sharp Memorial Hospital at Loew's Coronado Bay Resort, San Diego. Fri-Sun. 20 hrs. $425. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

INTERNAL MEDICINE

October 1-3—**Gastroenterology: Advances in Diagnosis and Management.** UCSF at Ana Hotel, San Francisco. Fri-Sun. 18 hrs. $430. Contact: UCSF.

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690. (415) 541-0900.

CPMC: California Pacific Medical Center
Contact: Continuing Education, California Pacific Medical Center, PO Box 7999, San Francisco 94120. (415) 923-3441.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Herbert M. Thomas, MD, MPH, Director of CME, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th St, Los Angeles 90059. (213) 603-3183.

LLU: Loma Linda University
Contact: James J. Couperus, MD, Associate Dean for Educational Affairs, Loma Linda University School of Medicine, Loma Linda 92350.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Medical School Office Building, Suite X-365, Stanford 94305-6114. (415) 723-5594.

UCD: University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, 2701 Stockton Blvd, Sacramento 95817. (916) 734-5390.

UCI: University of California, Irvine
Contact: Melvin I. Marks, MD, Director, Memorial/UCI Center for Health Education, Long Beach Memorial Medical Center, 2801 Atlantic Ave, PO Box 1428, Long Beach, California 90801-1428. (213) 595-3811.

UCLA: University of California, Los Angeles Extension
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, PO Box 24902, UCLA, Los Angeles 90024. (310) 825-8423.

UCSD: University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (619) 534-3940.

UCSF: University of California, San Francisco
Contact: Janet Johnson, Administrative Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 476-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 1975 Zonal Ave, KAM314, Los Angeles 90033. (800) 872-1119.

October 14-16—**Recent Advances in Pulmonary and Critical Care Medicine.** UCSF at Ana Hotel, San Francisco. Thurs-Sat. 16 hrs. $415. Contact: UCSF.

February 3-5—**17th Annual Neurology for the Non-Neurologists.** UCSD at Pan Pacific Hotel, San Diego. Thurs-Sat. 21 hrs. $450. Contact: Edith Bookstein, PO Box 2586, La Jolla 92038. (619) 454-3212.

February 5—**New Advances in Inflammatory Bowel Disease.** Scripps Clinic and Research Foundation at Green Hospital Amphitheater. Sat. 7 hrs. $140. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

OB/GYN

October 2-3—**Ultrasound Update.** UCD at Red Lion Hotel, Sacramento. Sat-Sun. 10 hrs. $190-$235. Contact: UCD.

November 20—**Infertility Update VII.** Scripps Clinic and Research Foundation, La Jolla. Sat. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

December 2-4—**Obstetrics and Gynecology Conference.** University of Nebraska at Bally's Las Vegas. Thurs-Sat. $275. Contact: University of Nebraska Medical Center, 600 S 42nd St, Omaha, NE 68198-5651. (402) 559-4152 or (800) 642-1095.

OCCUPATIONAL/ENVIRONMENTAL

October 25-29—**Occupational and Environmental Medicine.** UCSF at Miyako Hotel, San Francisco. Mon-Fri. 40 hrs. $700. Contact: UCSF.

ONCOLOGY

October 2—**Biologic Therapy in the Treatment of Human Malignancies.** UCLA at Hotel Nikko, Beverly Hills. Sat. 5.75 hrs. Contact: UCLA Extension.

October 23—**Biologic Agents of Solid Tumors.** UCD at Cancer Auditorium, Sacramento. Sat. Contact: UCD.

October 25-27—**17th Annual Cancer Symposium.** Scripps Memorial Hospital at Sheraton Harbor Island Hotel, San Diego. Mon-Wed. 20 hrs. $390. Contact: Cancer Symposium Conference Office, PO Box 16502, Irvine 92713-6338. (800) 321-6338.

November 4-5—**Growth Control, Signal Transduction and Oncogenesis.** UCLA at Beverly Hilton Hotel, Beverly Hills. Thurs-Sat. 12.75 hrs. $113-$150. Contact: UCLA Extension.

November 5-6—**American College of Surgeons: Cancer Management Course.** UCD at Cancer Center Auditorium, Sacramento. Fri-Sat. 13 hrs. $400. Contact: UCD.

December 5—**Tumors of the Female Genital Tract.** California Tumor Tissue Registry at Ritz-Carlton Hotel, San Francisco. Sat. 8 hrs. $55. Contact: California Tumor Tissue Registry, c/o Loma Linda University, 11021 Campus Ave, AH 335, Loma Linda 92354. (909) 824-4788.

February 21-23—**Clinical Hematology and Oncology: 1994.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Mon-Wed. 18 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

OPHTHALMOLOGY

September 18—**General Medicine Update for Ophthalmologists.** UCD at Cancer Center Auditorium, Sacramento. Sat. Contact: UCD.

October 16—**Annual Ophthalmology Update: 1993.** UCD at Cancer Auditorium at Sacramento. Sat. Contact: UCD.

ORTHOPEDICS

September 18—**Practical Orthopedics.** Auburn Faith Community Hospital. Sat. Contact: Joan Dillon, 2800 L St, Sacramento 95816. (916) 733-3883.

September 29-October 2—**6th Annual Comprehensive Foot and Ankle Course.** American Academy of Orthopedic Surgeons at Sheraton Palace Hotel/Summit Health Education Center, San Francisco. Wed-Sat. Contact: AAOS, 6300 N River Rd, Rosemont, IL 60018-4262. (800) 346-2207.

October 18-20—**The Knee and Shoulder in Sports.** American College of Sports Medicine at Westin Maui, Kaanapali Beach, Maui, Hawaii. Mon-Wed. 13 hrs. $300. Contact: Stuart Zeman, MD, (800) 346-3277.

October 29-30—**Revision Total Hip in the 1990s.** American Academy of Orthopedic Surgeons at US Grant Hotel, San Diego. Fri-Sat. Contact: AAOS, 6300 N River Rd, Rosemont, IL 60018-4262. (800) 346-2207.

(Continued on Page 246)

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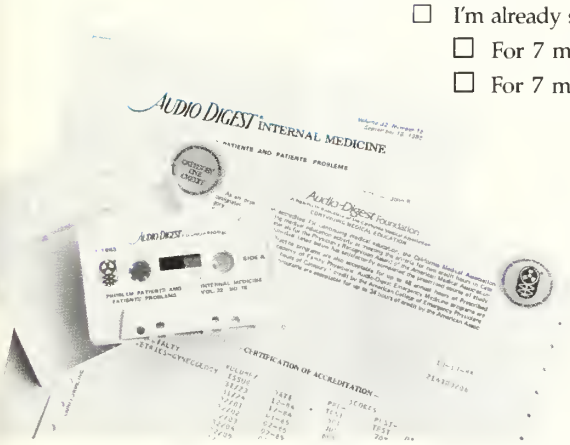

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CONTINUING MEDICAL EDUCATION

(Continued from Page 244)

November 5-9—**Fractures of the Pelvis and Acetabulum.** American Academy of Orthopedic Surgeons at Marriott's Rancho Las Palmas Resort and Country Club Annenberg Center, Eisenhower Medical Center, Rancho Mirage. Fri-Tues. Contact: AAOS, 6300 N River Rd, Rosemont, IL 60018-4262. (800) 346-2207.

December 1-4—**Cost Effective Back Care.** American Back Society at San Francisco Hilton & Towers. Wed-Sat. Contact: Aubrey Swartz, 2647 E 14th St, Ste 401, Oakland 94601. (510) 536-9929.

December 3-5—**Review and Update for Practicing Orthopaedic Surgeons.** American Academy of Orthopedic Surgeons at Sheraton Palace Hotel, San Francisco. Fri-Sun. Contact: AAOS, 6300 N River Rd, Rosemont, IL 60018-4262. (800) 346-2207.

December 8-12—**American Back Society Meeting.** American Back Society at Hyatt Regency Embarcadero, San Francisco. Wed-Sun. Contact: ABS, 2647 E 14th St, Ste 401, Oakland 94601. (510) 536-9929.

OTOLARYNGOLOGY

September 19-24—**Temporal Bone Dissection Course.** House Ear Institute. Sun-Fri. 53 hrs. $875-$1,100. Contact: Antonio De la Cruz, 2100 W Third St, Los Angeles 90057. (213) 483-4431 ext. 7079.

November 4-6—**The San Francisco Otology, Neurotology, and Skull Base Surgery Update—1993.** UCSF at Ritz-Carlton Hotel, San Francisco. Thurs-Sat. 22 hrs. $395. Contact: UCSF.

PATHOLOGY

October 2—**33rd Annual Scientific Symposium on Kidney Disease.** National Kidney Foundation of Southern California at Stouffer Esmeralda Resort, Indian Wells. Sat. $125. Contact: Sylvie Tarro, (310) 641-8152.

October 25-29—**19th Annual Lukes Conference: Diagnostic Approaches to Lymphoproliferative Disorders.** Fri-Tues. 27 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

PEDIATRICS

September 18—**Pediatric Update.** Sutter Community Hospitals, Sacramento. Sat. Contact: Lynne MacRae, 2800 L St, Sacramento 95816. (916) 733-3883.

January 24-28—**San Diego Conference on Responding to Child Maltreatment.** Children's Hospital San Diego at Town and Country Hotel, San Diego. Mon-Fri. $390. Contact: Center for Child Protection, 8001 Frost St, San Diego 92123. (619) 395-4950.

PSYCHIATRY

September 18—**Beyond the Basics II.** San Francisco Academy of Hypnosis Education at Letterman Medical Center, San Francisco. Sat. $125. Contact: Jan Brooks, 615 27th Ave, San Francisco 94131. (415) 282-3399.

October 5-November 16—**Hypnotherapy with Sexually Abused Patients: Treatment Strategies, Techniques and Ethical Issues.** UCLA at Westwood United Methodist Church. Tuesdays. 14 hrs. $160. Contact: UCLA Extension.

February 26—**1994 Sleep Medicine Update.** Scripps Clinic and Research Foundation at La Jolla. Sat. 7 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

RADIOLOGY

October 3-6—**Current Concepts of Magnetic Resonance.** Stanford and Duke University at Ritz-Carlton Resort Hotel, Laguna Niguel. Sun-Wed. 22.75 hrs. $450-$550. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

October 18-20—**Radiology for the Non-Radiologist.** UCSD at Hyatt Regency, San Diego. Mon-Wed. 20 hrs. $450. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

October 18-22—**Women's Imaging: An Update on Women's Health Issues.** Western Pennsylvania Hospital and University of Alabama at Birmingham at Ritz-Carlton Hotel, Laguna Niguel. Mon-Fri. 20 hrs. $525. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

October 23-24—**MRI of the Musculoskeletal System.** UCSD at Hotel del Coronado, San Diego. Sat-Sun. 9 hrs. $275. Contact: UCSD.

October 25-29—**18th Annual San Diego Postgraduate Radiology Course.** UCSD at Hotel del Coronado, San Diego. Mon-Fri. 25 hrs. $595. Contact: UCSD.

October 29-31—**Annual Interventional Radiology Course.** UCSD at Hotel del Coronado, San Diego. Fri-Sun. 16 hrs. $375. Contact: UCSD.

November 12-14—**Advanced Seminars in Diagnostic Imaging.** UCSD at Ritz-Carlton, Laguna Niguel. Fri-Sun. 20 hrs. $500. Contact: UCSD.

January 17-19—**Neuroradiology Update.** Stanford University Medical Center at Ritz-Carlton, Laguna Niguel. Mon-Wed. 17.5 hrs. $450. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

January 20-23—**Breast Imaging Update.** Stanford University Medical Center at Ritz-Carlton Hotel, Laguna Niguel. Thurs-Sun. 16 hrs. $450. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

February 14-18—**Contemporary Diagnostic Imaging.** Stanford University Medical Center at Ritz-Carlton Resort Hotel, Kapalua, Hawaii. Mon-Fri. 20.5 hrs. $550. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925.

RISK MANAGEMENT

September 27-28—**High Risk Emergency Medicine: Preventing Malpractice.** CAL/ACEP at Las Vegas, Nevada. Mon-Tues. 15 hrs. $345-$495. Contact: Kathy Hester, (800) 451-7475.

VASCULAR DISEASE

October 4-8—**A Comprehensive Review of What's New in Vascular Surgery.** UCLA at Miramar Sheraton Hotel, Santa Monica. Mon-Fri. 34 hrs. $487-$650. Contact: UCLA Extension.

GENERAL/MULTIDISCIPLINARY

September 25—**Women's Health.** University of the Pacific, Stockton. Sat. Contact: Catherine Davis, 2800 L St, Sacramento 95816. (916) 733-3883.

October 14-17—**Women in Medicine.** UCSD at San Diego Hilton. Thurs-Sun. 15 hrs. $300. Contact: UCSD.

October 16—**12th Annual Sharrer Symposium: Change and Stress in Medicine—The Modern Physician.** Kaweah Delta District Hospital at Radisson Hotel, Visalia. Sat. 4 hrs. Contact: Susan Delgado, Continuing Education, (209) 625-7308.

October 27-31—**CME/Golf Meeting.** Nevada Academy of Family Physicians Las Vegas Chapter at Rio Hotel, Las Vegas. Wed-Sun. 23 hrs. $75. Contact: Barbara Bolling, PO Box 27713, Las Vegas, NV 89126-1713. (702) 647-0117.

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COLORADO

This listing of continuing medical education programs in Colorado is compiled by the Denver Medical Society. To list CME programs here, please send information at least two months in advance to: Mr Robert L. Kennedy, Denver Medical Society, 1850 Williams Street, Denver, CO 80218; or telephone (303) 377-1850.

Brochures, course information, and registration forms are available from the contact person or organization.

September 20-21—**Pediatric Nursing Traineeship Program.** Children's Hospital, Denver, Mon-Tues. Contact: Outreach Office, (303) 861-6668.

September 21-22, 28-29—**Comprehensive Perinatal Nursing Course.** Children's Hospital at University Hospital, Denver. Tues-Wed. Contact: Trish Beachy, (303) 270-8376.

September 23-25—**The Penrose Cancer Conference: Neoplastic Diseases of the Breast and Ovary.** The Penrose-St Francis Healthcare System at the Broadmoor Hotel, Colorado Springs. Thurs-Sat. Contact: Deborah Hood, Penrose-St Francis Health Care System, PO Box 7021, Colorado Springs 80933-9939. (719) 630-5716.

(Continued on Page 252)

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(Continued from Page 240)

382 **Clinical Teratology**
ASHER ORNOY, MD, and JUDY ARNON, PhD
From the Department of Anatomy and Embryology, Laboratory of Teratology, and the Jerusalem Institute of Child Development, Hebrew University-Hadassah Medical School, Jerusalem, Israel.

391 **Ethical Considerations in Prenatal Diagnosis**
ELENA A. GATES, MD
From the Department of Obstetrics, Gynecology and Reproductive Sciences, University of California, San Francisco, School of Medicine.

396 **Ethical Issues in Recommending and Offering Fetal Therapy**
FRANK A. CHERVENAK, MD, and LAURENCE B. McCULLOUGH, PhD
From the Department of Obstetrics and Gynecology, Division of Maternal-Fetal Medicine, New York Hospital-Cornell Medical Center, New York, New York, and the Department of Medicine and Community Medicine, Center for Ethics, Medicine, and Public Issues, Baylor College of Medicine, Houston, Texas.

400 **Ethics of Fetal Tissue Transplantation**
LEE M. SANDERS; LINDA GIUDICE, MD, PhD; and THOMAS A. RAFFIN, MD
From the Stanford University Center for Biomedical Ethics, Stanford University School of Medicine, Stanford, California.

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426 **Western State Medical Associations' Meetings**

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Dihydrocodeine Bitartrate ..... 16 mg

(**Warning:** May be habit forming.)

Acetaminophen..... 356.4 mg

Caffeine ..... 30 mg

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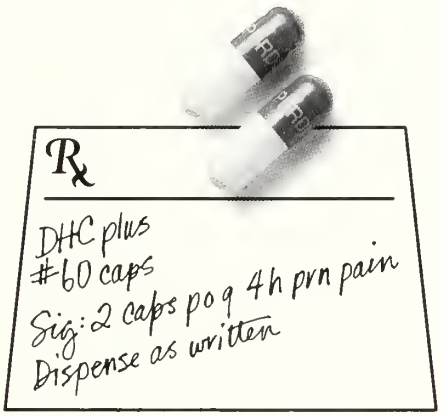

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Usage In Children: Since there is no experience in children who have received this drug, safety and efficacy in children have not been established.

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Dihydrocodeine can produce drug dependence of the codeine type and therefore has the potential of being abused. Psychic dependence, physical dependence, and tolerance may develop upon repeated administration of dihydrocodeine, and it should be prescribed and administered with the same degree of caution appropriate to the use of other oral narcotic-containing medications.

OVERDOSAGE: Dihydrocodeine: Signs and Symptoms: Serious overdose with DHC Plus™ is characterized by respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), extreme somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, and sometimes bradycardia and hypotension. In severe overdosage, apnea, circulatory collapse, cardiac arrest and death may occur.

Treatment: Primary attention should be given to the re-establishment of adequate respiratory exchange through provision of a patent airway and the institution of assisted or controlled ventilation. The narcotic antagonist naloxone is a specific antidote against respiratory depression which may result from overdosage or unusual sensitivity to narcotics, including codeine. Therefore, an appropriate dose of naloxone hydrochloride should be administered, preferably by the intravenous route and simultaneously with efforts at respiratory resuscitation. Since the duration of action of dihydrocodeine may exceed that of the antagonist, the patient should be kept under continued surveillance and repeated doses of the antagonist should be administered as needed to maintain adequate respiration.

An antagonist should not be administered in the absence of clinically significant respiratory or cardiovascular depression.

Oxygen, intravenous fluids, vasopressors, and other supportive measures should be employed as indicated.

Gastric emptying may be useful in removing unabsorbed drug.

Acetaminophen: Signs and Symptoms: In acute acetaminophen overdosage, dose-dependent, potentially fatal hepatic necrosis is the most serious adverse effect. Renal tubular necrosis, hypoglycemic coma, and thrombocytopenia may also occur. In adults, hepatic toxicity has rarely been reported with acute overdoses of less than 10 grams and fatalities with less than 15 grams. Importantly, young children seem to be more resistant than adults to the hepatotoxic effect of an acetaminophen overdose. Despite this, the measures outlined below should be initiated in any adult or child suspected of having ingested an acetaminophen overdose.

Early symptoms following a potentially hepatotoxic overdose may include: nausea, vomiting, diaphoresis, and general malaise. Clinical and laboratory evidence of hepatic toxicity may not be apparent until 48 to 72 hours post-ingestion.

Treatment: The stomach should be emptied promptly by lavage or by induction of emesis with syrup of ipecac. Patients' estimates of the quantity of a drug ingested are notoriously unreliable. Therefore, if an acetaminophen overdose is suspected, a serum acetaminophen assay should be obtained as early as possible, but no sooner than four hours following ingestion. Liver function studies should be obtained initially and repeated at 24-hour intervals.

The antidote, N-acetylcysteine, should be administered as early as possible, preferably within 16 hours of the overdose ingestion for optimal results, but in any case within 24 hours. Following recovery, there are no residual, structural or functional hepatic abnormalities.

DOSAGE AND ADMINISTRATION: Dosage should be adjusted according to the severity of the pain and the response of the patient. DHC Plus™ is given orally. The usual adult dosage is two capsules every (4) hours as needed for pain.

CAUTION: Federal law prohibits dispensing without prescription.

REFERENCES

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(Continued from Page 246)

September 24—**Health Care Reform: The Heart of the Matter.** St Anthony Hospitals and Rocky Mountain Heart Consortium at Scanticon Hotel & Conference Center, Englewood. Fri. Contact: Rocky Mountain Heart Consortium, (303) 393-3951.

October 14-16—**Rural Perinatal Traineeship Program.** Children's Hospital, Denver. Thurs-Sat. Contact: Outreach Office, (303) 861-6668.

November 5-6—**16th Annual Perinatal Conference.** Children's Hospital of Denver at Laramie, Wyoming. Fri-Sat. Contact: Conference Office, (303) 861-6946 or (800) 225-0010.

November 11-13—**Rural Perinatal Traineeship Program.** Children's Hospital, Denver. Thurs-Sat. Contact: Outreach Office, (303) 861-6668.

December 18—**Computers in Medicine.** Rose Medical Center at Hotel L'Ostello, Vail. Sat. Repeated weekly through April 23, 1994, at either Hotel L'Ostello, Vail, or Hotel Wildwood, Snowmass Village. Contact: Bernard Karshmer, (800) 525-5810.

January 27-29—**Contemporary Management of Unstable Coronary Syndromes.** Department of Veterans Affairs at Beaver Run Resort, Breckenridge. Thurs-Sat. Contact: Karen Babcock, (303) 393-2826.

January 29-February 5—**Internal Medicine Conference.** Rose Medical Center at Radisson Resort, Vail. Sat-Sat. Contact: Bernard Karshmer, (800) 525-5810.

February 5-12—**General Surgery Conference.** Rose Medical Center at Radisson Resort, Vail. Sat-Sat. Contact: Bernard Karshmer, (800) 525-5810.

February 12-19—**Emergency Medicine Conference.** Rose Medical Center at Radisson Resort, Vail. Sat-Sat. Contact: Bernard Karshmer, (800) 525-5810.

February 12-19—**Psychiatry Conference.** Rose Medical Center at Radisson Resort, Vail. Sat-Sat. Contact: Bernard Karshmer, (800) 525-5810.

February 19-26—**Neurology Conference.** Rose Medical Center at the Antlers Hotel, Vail. Sat-Sat. Contact: Bernard Karshmer, (800) 525-5810.

February 19-26—**Obstetrics and Gynecology Conference.** Rose Medical Center at Radisson Resort, Vail. Sat-Sat. Contact: Bernard Karshmer, (800) 525-5810.

February 26-March 5—**Pediatrics Conference.** Rose Medical Center at Radisson Resort, Vail. Sat-Sat. Contact: Bernard Karshmer, (800) 525-5810.

February 26-March 5—**Infectious Disease Conference.** Rose Medical Center at the Antlers Hotel, Vail. Sat-Sat. Contact: Bernard Karshmer, (800) 525-5810.

March 5-12—**Primary Care Conference.** Rose Medical Center at Radisson Resort, Vail. Sat-Sat. Contact: Bernard Karshmer, (800) 525-5810.

March 5-12—**Minding the Body/Mending the Mind.** Rose Medical Center at the Antlers Hotel, Vail. Sat-Sat. Contact: Bernard Karshmer, (800) 525-5810.

March 6-11—**14th Annual Keystone ENT Conference.** University of Nebraska Medical Center at Keystone Resort, Keystone. Sun-Fri. Contact: U of Nebraska Continuing Education Center, (402) 559-4152.

March 12-19—**Sports Medicine Conference.** Rose Medical Center at Radisson Resort, Vail. Sat-Sat. Contact: Bernard Karshmer, (800) 525-5810.

March 12-19—**Urology Conference.** Rose Medical Center at Radisson Resort, Vail. Sat-Sat. Contact: Bernard Karshmer, (800) 525-5810.

March 19-26—**Cancer Treatment Conference.** Rose Medical Center at the Antlers Hotel, Vail. Sat-Sat. Contact: Bernard Karshmer, (800) 525-5810.

Tuesday Noon Conferences—**Various Topics in Medicine.** Lutheran Medical Center, Wheat Ridge. Contact: Jean A. Kline, (303) 425-2951.

Every Second Wednesday of the Month—**Cardiovascular Education Series.** St Anthony Hospitals at St Anthony Hospital, Denver. Contact: Rose Powell, (303) 629-3678.

Every Friday (except 4th Friday of month)—**Various Topics in Contemporary Medicine (Midday CME Series).** St Anthony Hospitals at St Anthony Hospital, Denver. Contact: Rose Powell, (303) 629-3678.

First Wednesday of Each Month—**Various Topics in Neurology.** Sponsored by the Colorado Society of Clinical Neurologists. Contact: Colorado Society of Neurologists, (303) 449-3566.

CONTACT INFORMATION

U of Colo—Contact, University of Colorado School of Medicine, Office of Continuing Medical Education, 4200 E. 9th Ave, Denver, CO. (303) 270-5195 or (800) 882-9153; FAX (303) 270-6761.

NEW MEXICO

Information, requests for accreditation, and items to be listed should be sent to the chair of the CME Committee, New Mexico Medical Society, 7770 Jefferson, Suite 400, Albuquerque, NM 87109, at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 828-0237.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

September 21-24—**The Medicolegal Investigation of Death-Forensic Science Seminar.** Sheraton Old Town Inn, Albuquerque. Tues-Fri. Contact: Suzanne Fetsco, Office of Medical Investigators, UNM School of Medicine, Albuquerque 87131-5091. (505) 277-3053.

October 1-2—**John N. Wilson, MD, Lectureship in Cardiology: Cardiology '93.** Albuquerque Hilton Hotel. Fri-Sat. Contact: Mary Boning, PO Box 26666, Albuquerque 87125-6666. (505) 841-1225.

October 2-3—**Pediatric Sports Medicine and Fitness.** Inn of the Mountain Gods, Mescalero/Ruidoso. Sat-Sun. Contact: Richard Rolston, MD, 4808 McMahon Blvd NW, #16, Albuquerque 87114. (505) 898-7898.

October 7-9—**10th Annual Santa Fe Colloquium on Cardiovascular Therapy.** Santa Fe. Thurs-Sat. Contact: American College of Cardiology Extramural Programs, 9111 Old Georgetown Rd, Bethesda, MD 20897-1448. (800) 257-4739.

October 16—**New Mexico Orthopaedic Association Annual Meeting: Sports Medicine.** Inn at Loretto, Santa Fe. Sat. Contact: Elsa Hall, 7770 Jefferson NE, #400, Albuquerque 87109. (505) 828-0237.

November 11-14—**Violence Education Conference. Theme: Teaching About Violence: Curricula, Values, Obstacles, and Solutions.** Sheraton Old Town Inn, Albuquerque. Thurs-Sun. Contact: Program Department, Society of Teachers of Family Medicine, PO Box 8729, Kansas City, MO 64114. (800) 274-2237.

CONTACT INFORMATION

UNM SOM—University of New Mexico School of Medicine, Office of CME, PO Box 713, Albuquerque 87131. (505) 277-3942.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. Accredited institutions wishing to list AMA Category 1 CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, UT 84102; or phone (801) 355-7477. For information on CME accreditation, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution.

September 22-25—**Utah Medical Association Annual Meeting.** University Park Hotel, Salt Lake City. Wed-Sat. Contact: UMA.

September 24—**Utah Psychiatric Association Semi-Annual Meeting.** University Park Hotel, Salt Lake City. Fri. Contact: UMA.

October 8-9—**Western Intermountain Neurological Organization.** University Park Hotel, Salt Lake City. Fri-Sat. Contact: UUSM.

(Continued on Page 254)

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(Continued from Page 252)

October 9—**Diabetes Mellitus: Real World Management for the Primary Care Physician.** Eccles Health Sciences Genetics Auditorium, University of Utah, Salt Lake City. Sat. Contact: UUSM

December 5-9—**Intensive Neuroradiology.** Marriott Hotel, Salt Lake City. Sun-Thurs. Contact: UUSM

February 7-11—**Surgical Pathology.** Yarrow Hotel, Park City. Mon-Fri. Contact: UUSM.

February 14-18—**Update in Clinical Microbiology and Immunology.** Yarrow Hotel, Park City. Mon-Fri. Contact: UUSM.

February 17-24—**37th Anesthesiology Update: Anesthesia and the Nervous System.** Snowbird Cliff Lodge. 1 week. Contact: UUSM.

February 23-27—**Physical Medicine and Rehabilitation Update.** Prospector Square Conference Center, Park City. Wed-Sun. Contact: UUSM.

February 27-March 2—**35th Annual OB/GYN Update.** Yarrow Hotel, Park City. Sun-Wed. Contact: UUSM.

March 2-5—**Surgical Oncology Update.** Yarrow Hotel, Park City. Wed-Sat. Contact: UUSM.

March 6-11—**Advances in Internal Medicine.** Cottonwood Center, Snowbird. Sun-Fri. Contact: UUSM.

March 8-12—**Microsurgery Workshop.** University Park Hotel, Salt Lake City. Thurs-Sat. Contact: UUSM.

March 11-12—**Western Intermountain Neurological.** University Park Hotel, Salt Lake City. Fri-Sat. Contact: UUSM.

MEDICAL GRAND ROUNDS

Weekly—Internal Medicine Grand Rounds, Psychiatry Grand Rounds, OB/GYN Grand Rounds, Pediatric Grand Rounds. Contact: UUSM, Office of CME, (801) 581-8664.

SPONSORS OF COURSES—ABBREVIATIONS

CH:	Castleview Hospital, 300 N Hospital Dr, Price 84501. (801) 637-4800.
CS:	Charter Summit Hospital, 175 W 7200 South, Midvale 84047. (801) 561-8181.
DM	Dixie Medical Center, 544 S 400 East, St George 84770. (801) 634-4000.
ETS:	Emergency Training Services, 777 N 390 East, American Fork 84003. (801) 763-3555.
FHP:	FHP of Utah, 35 W Broadway, Salt Lake City 84101. (801) 355-1234.
ITS:	Intermountain Thoracic Society, 1616 S 11th East, Salt Lake City 84105. (801) 484-4456.
LDSH:	LDS Hospital, 8th Ave and "C" St, Salt Lake City 84143. (801) 321-1100.
LRH:	Logan Regional Hospital, 1400 N 5th East, Logan 84321. (801) 752-2050.
MVH	Mountain View Hospital, 1000 E Highway 6, Payson 84651. (801) 465-9201.
OSS:	Ogden Surgical-Medical Society, PO Box 9311, Ogden 84409.
PCMC	Primary Children's Medical Center, 100 N Medical Dr, Salt Lake City 84113. (801) 588-2000
PVH	Pioneer Valley Hospital, 3460 S 4155 West, West Valley City 84120. (801) 968-9061.
UMIA	Utah Medical Insurance Association, 540 E 500 South, Salt Lake City 84102. (801) 531-0375.
UMA	Utah Medical Association, 540 E Fifth South, Salt Lake City 84102. (801) 355-7477.
UOS:	Utah Ophthalmological Society, 540 E 500 South, Salt Lake City 84102. (801) 355-7477.
USH:	Utah State Hospital, PO Box 270, Provo 84603-0270. (801) 373-4400.
UUSM	University of Utah School of Medicine, Office of Continuing Medical Education, 50 N Medical Dr, Salt Lake City 84132. (801) 581-8664
VAMC:	Veterans Administration Medical Center, 500 Foothill Dr, Salt Lake City 84148. (801) 582-1565.

WASHINGTON

The listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here, please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 1100, Seattle, WA 98121; or phone (206) 441-9762 or (800) 552-0612.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

September 17—**Family Practice Day.** Renton. Fri. Contact: Valley Medical Center, (206) 228-3440.

September 22-25—**North Pacific Pediatric Society.** Vancouver, BC. Wed-Sat. Contact: Children's, (206) 258-6322.

September 23—**Domestic Violence.** Everett. Thurs. Contact: PNMEH, (206) 258-6322.

September 24-25—**Diabetes Update.** Seattle. Fri-Sat. Contact: U/W.

September 30-October 1—**Atherosclerosis and Restenosis.** Seattle. Thurs-Fri. Contact: U/W.

October 1—**Pharmacology.** Tacoma. Fri. Contact: Multicare, (206) 552-1221.

October 1—**Harkins Videoedoscopy Seminar With the Strauss Lecture.** Fri. Contact: U/W.

October 8-9—**Society for Pediatric Pathology.** Seattle. Wed-Fri. Contact: Children's Hospital, (206) 526-2501.

October 8-9—**Pulmonary Medicine for the Clinician.** Seattle. Fri-Sat. Contact: U/W.

October 13—**Hypertension.** Wed. Contact: U/W.

October 15—**The Walking Wounded—Acute Care Outside the ICU.** Everett. Fri. Contact: PNMEH, (206) 258-6322.

October 20—**Perinatology Day.** Tacoma. Wed. Contact: Multicare, (206) 552-1221.

October 22-23—**Adolescent Medicine.** Seattle. Thurs-Fri. Contact: Children's Hospital, (206) 526-2501.

October 23—**Pediatric Endocrinology.** Tacoma. Fri. Contact: Multicare, (206) 552-1221.

October 23—**Treatment of CNS Tumors: Stereotactic Radiosurgery.** Sat. Contact: U/W.

October 27—**Perinatology Conference.** Tacoma. Wed. Contact: Multicare, (206) 552-1221.

November 4-5—**Drug Therapy.** Seattle. Thurs-Fri. Contact: U/W.

November 18-19—**Diabetes Update.** Thurs-Fri. Contact: U/W.

November 19—**Advances in Therapeutics for the Clinician.** Renton. Fri. Contact: VMC, (206) 228-3440.

December 2-4—**American College of Physicians.** Seattle. Thurs-Sat. Contact: U/W.

December 9-12—**9th Infectious Disease Conference.** Everett. Tues-Sat. Contact: PNMEH, (206) 258-6322.

December 10-11—**Mental Health Update.** Fri-Sat. Contact: U/W.

December 10-11—**Regional Musculoskeletal Conference.** Seattle. Fri-Sat. Contact: U/W.

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104. (206) 223-5953.

PCMS CME—Contact: Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

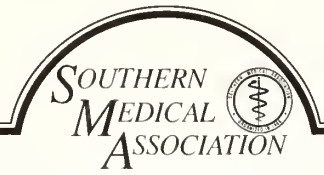
U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 223-6898.

WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Suite 1100, Seattle, WA 98121. (206) 441-9762.

WYOMING

October 29-30—**16th Annual Perinatal Conference.** Children's Hospital of Denver at Laramie. Fri-Sat. Contact: Conference Office, (303) 861-6946 or (800) 225-0010. ◆



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FEE: SMA Member-$75; Nonmember-$200.
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DECEMBER 3-4, 1993

SPA PSYCHIATRIC UPDATE
LOCATION: Birmingham, Alabama
SPECIALTY: Psychiatry
CME CREDIT: AMA Category I
FEE: SMA/SPA Member-$100; Nonmember-$200; Nonphysician-$50

DECEMBER 3-5, 1993

BURN SEMINAR
LOCATION: Orlando, Florida
SPECIALTY: Burn Center Directors and Health Care Professionals
CME CREDIT: AMA Category I
FEE: All Participants $75

JANUARY 28-30, 1994

KNEE SYMPOSIUM
LOCATION: Orlando, Florida
SPECIALTY: Orthopaedics
CME CREDIT: AMA Category I
FEE: SMA Member-$150; Nonmember-$300; Residents/Fellows-$50

JANUARY 29-FEBRUARY 5, 1994

PREVENTIVE MEDICINE
LOCATION: Tucson, Arizona
SPECIALTY: Primary Care
CME CREDIT: AMA Category I
FEE: SMA Member-$475; Nonmember-$600; Nonphysician-$300

FEBRUARY 2-4, 1994

ENT UPDATE
LOCATION: St. Thomas, Virgin Islands
SPECIALTY: Otolaryngology
CME CREDIT: AMA Category I
FEE: SMA Member-$475; Nonmember-$600; Nonphysician-$300

FEBRUARY 11-13, 1994

THE ATHLETIC PATIENT
LOCATION: Fort Lauderdale, Florida
SPECIALTY: Primary Care, Orthopaedics, Internal Medicine
CME CREDIT: AMA Category I–14 hours
FEE: SMA Member-$375; Nonmember-$500; Nonphysician-$250

For more information, call Michelle Williamson, Southern Medical Association, 800-423-4992 or 205-945-1840—TODAY!

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Manuscripts should be sent to the Editor, Linda Hawes Clever, MD, *The Western Journal of Medicine*, 221 Main Street, San Francisco, California 94105. Manuscripts must be original, not previously published, and not under consideration by another publication. If preliminary data were included in another presentation or publication, this should be noted in the cover letter and a copy of that publication should be included.

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- Lessons From the Practice: 1,000 words
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All manuscripts will be subject to peer review.

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All authors must sign the letter of transmittal, with one author designated as correspondent and his or her name, address, and telephone number included.

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References

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CHECKLIST

- Original manuscript and 2 copies
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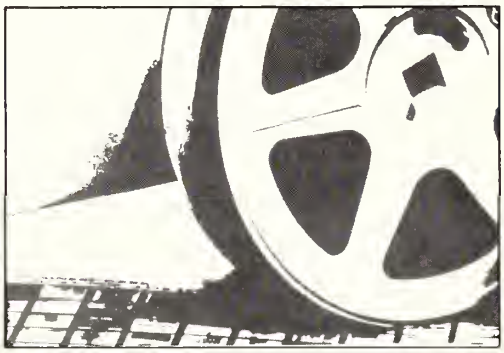

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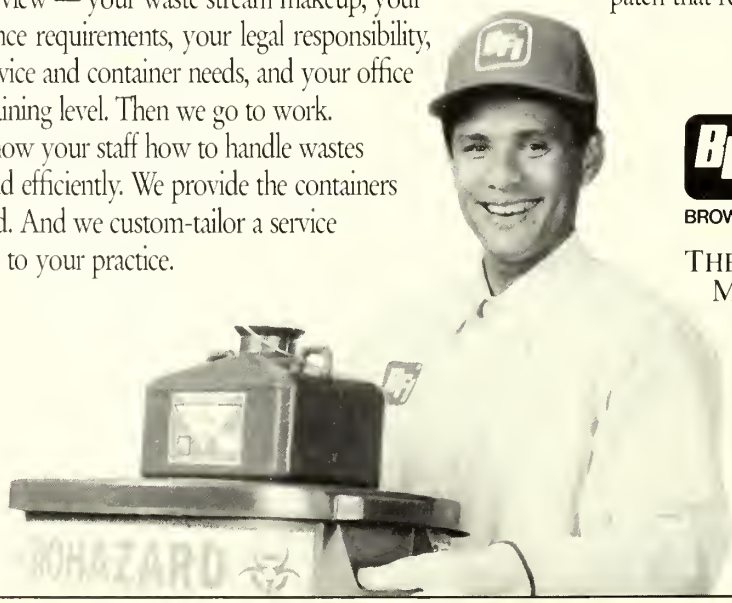

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Fetal Medicine

As the mysteries of fetal development unfold, opportunities abound and questions proliferate. This special issue of The Western Journal of Medicine, with authors so capably recruited and papers so carefully edited, is the work of James Goldberg, MD, Associate Professor of Obstetrics, Gynecology and Reproductive Sciences at the University of California, San Francisco. Much of the issue addresses the question, "Can we?" From basic research and technical standpoints, the answer is "Yes," "Sometimes," "Almost," or "We hope so." From the financing standpoint, the answer is, "So far," "It depends," or "We will know when controlled studies on cost-effectiveness are conducted." Clearly, however, we have the nascent ability to diagnose and treat fetal conditions. These advances are dramatic testimony to basic, animal, and human research and touching testimony to the courage and yearnings of parents—mothers, especially, because they knowingly take risks—and of clinical scientists.

Where do we go from here? We need more science, more trials, more rigorous study of "Does it make a difference?" and "To whom?" At the same time, we and other members of society ask, "Should we?" and "Ought we?" To help answer these questions, the viewpoints of both scientists and ethicists are well represented in this special issue. As with all genuinely complex issues, discussions will be never-ending. This is a beginning.

This issue is more than a status report. It documents triumphs, asks good questions, and maps the course for future research and thinking.

LINDA HAWES CLEVER, MD

Introduction

Advances in maternal fetal medicine and reproductive genetics have served to focus attention on the fetus. While we still place much concern on the condition of the pregnant woman, the effects of her condition or therapy on the fetus now are also considered. This has been an important change in outlook, brought about primarily by our improved ability to "examine" the fetus in utero, which has opened new areas of investigation in the evolving field of "fetal medicine."

Initially, this improved ability to examine the fetus made possible advances in diagnosing fetal congenital anomalies. These included the analysis of a variety of fetal tissues including amniotic fluid cells, chorionic villi, blood, liver, skin, and muscle. Another important advance was identifying fetal structural anomalies by high resolution ultrasound. These approaches allowed many couples the possibility of only having unaffected offspring. It also identified those fetuses that would need early surgical or metabolic therapy so that they might be delivered in tertiary care centers. While these advances were substantial, it was not until the advent of fetal therapy that the field of fetal medicine became firmly established.

Fetal therapy is still in its infancy. Approaches to repairing structural malformations and treating metabolic disorders are being attempted in several centers worldwide. Because of the highly experimental nature of many of these treatments, only a few centers are undertaking them. This has necessitated worldwide referrals and consultations taking place by phone, overnight courier, and the internet.

This special issue of The Western Journal of Medicine was organized to discuss these issues and present the readers with a status report. Investigators discuss both the current state of fetal diagnosis and innovations in fetal therapy. The other area that receives major focus is one that is vitally important in this field—the ethical and legal status of a fetus and fetal tissues. As one can readily see, we are not only dealing with the status of the developing fetus, but of the mother as well. It is evident that much serious thought has gone into examining these issues.

I wish to thank Holly Smith, MD, and Linda Clever, MD, for giving me the opportunity to organize this special issue. I hope they ask me to do an update in ten years. I also wish to thank all of the authors for the incredible amount of work that they put into their manuscripts.

JAMES D. GOLDBERG, MD
Special Issue Editor
Associate Professor of Obstetrics, Gynecology and Reproductive Sciences
University of California, San Francisco, School of Medicine

Amniocentesis and Chorionic Villus Sampling

LEE P. SHULMAN, MD, *and* SHERMAN ELIAS, MD, *Memphis, Tennessee*

Amniocentesis and chorionic villus sampling have been shown through prospective, multicenter trials to be safe and effective methods of prenatal diagnosis; accordingly, a knowledge of these tests is important for those physicians who care for women during their childbearing years. We review the indications, techniques, safety, accuracy, and efficacy of amniocentesis and chorionic villus sampling and compare the advantages and disadvantages of each diagnostic test. This review should enable physicians to provide appropriate counseling and information to women at increased risk for fetal abnormalities detectable by either of these procedures.

(Shulman LP, Elias S: Amniocentesis and chorionic villus sampling, *In* Fetal Medicine [Special Issue]. West J Med 1993; 159:260-268)

Invasive prenatal diagnosis of fetal abnormalities has become an integral part of obstetrics and perinatal medicine. Midtrimester amniocentesis has traditionally been the most common technique used for invasive prenatal diagnosis; however, the desire for first-trimester prenatal diagnosis has led to the development and eventual integration of chorionic villus sampling into the invasive prenatal diagnostic repertoire. In addition, the desire to diagnose prenatal abnormalities earlier in pregnancy has led to the increasing use of amniocentesis in the first and early second trimesters.

We review the uses of amniocentesis, both traditional and early, and chorionic villus sampling for the prenatal diagnosis of fetal abnormalities in the first and second trimesters of pregnancy. Because these two diagnostic tests have become integral to obstetric practice in the United States, familiarity with the techniques, risks, and limitations of these tests is critical to those physicians who care for women of childbearing age.

Amniocentesis

Over the past two decades, second-trimester amniocentesis has become a standard procedure for the diagnosis of fetal genetic abnormalities. Cytogenetic, enzymatic, and DNA analyses can be done on cells obtained from amniotic fluid. In addition, levels of α-fetoprotein (AFP) and acetylcholinesterase (AChE) in the amniotic fluid can be measured to diagnose neural tube defects (such as spina bifida and anencephaly) and anterior abdominal wall defects (for example, omphalocele and gastroschisis) prenatally. Thus, amniocentesis is applicable for the prenatal diagnosis of many fetal abnormalities.

Technique

Conventional genetic amniocentesis is usually performed between 14 and 20 weeks' gestation ("menstrual weeks") to evaluate a fetus for chromosome abnormalities, neural tube defects, and other detectable genetic and acquired disorders (Table 1). An ultrasound examination should be done immediately before amniocentesis to evaluate fetal number and viability, confirm gestational age, assess placental location, and estimate amniotic fluid volume. We routinely perform a detailed fetal anatomic survey. In addition, a complete counseling session should precede amniocentesis or any other prenatal diagnostic test; indications for testing and the risks, benefits, and limitations of the prenatal test should be reviewed in detail and in language understandable by the patient.

Once the preoperative ultrasound examination and counseling are completed, a site is selected for inserting the needle into the amniotic cavity. Close attention should be paid to the location of the small bowel and bladder to avoid puncturing them. The needle insertion site is then cleansed with an iodine-based solution and draped with sterile towels. Some obstetricians use a local anesthetic, such as 5 ml of a 1% solution of lidocaine hydrochloride, before inserting the needle, but this is usually unnecessary.

We prefer a 22-gauge spinal needle and recommend no larger than a 20-gauge needle to do amniocentesis. The needle is inserted transabdominally into the amniotic cavity under continuous ultrasonographic guidance (Figure 1).[1] The needle should be inserted with one smooth, continuous motion until the needle tip is within the amniotic cavity. In some cases, a gentle "pop" can be felt by

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ABBREVIATIONS USED IN TEXT

AChE = acetylcholinesterase
AFP = α-fetoprotein
CVS = chorionic villus sampling

the obstetrician when the needle tip enters the amniotic cavity; however, this sensation does not always signal entry into the amniotic cavity, especially when the amniocentesis is performed before 14 weeks' gestation. Once the needle tip is in the amniotic cavity, the needle stylet is removed and a syringe is attached to the needle hub (Figure 2).[2]

Approximately 1 ml of amniotic fluid is aspirated initially; the syringe and this small amount of fluid are discarded to reduce the risk of specimen contamination by maternal cells. For second-trimester amniocentesis done between 14 and 20 weeks inclusive (that is, conventional amniocentesis), 20 to 30 ml of amniotic fluid is usually aspirated. Failure to aspirate amniotic fluid is most commonly due to membrane "tenting." When this occurs, the needle appears by ultrasonography to be within the amniotic cavity, but the needle tip has not penetrated the amniotic sac. This occurs more frequently with amniocentesis performed before 14 weeks' gestation because amnion and chorion are usually not fused early in gestation. Other causes of aspiration failure include tissue blockage of the needle tip and juxtaposition of the needle tip to fetal structures or membranes.

Once fluid aspiration is completed and the needle has been removed from the amniotic cavity, a cursory ultrasound examination is done to confirm fetal cardiac activity and to look for evidence of bleeding from the placenta, umbilical cord, or fetus. We administer 300 μg of Rh immune globulin to all unsensitized, Rh-negative patients, regardless of whether the placenta has been traversed by the needle. The patient may resume all normal activities following amniocentesis, but common sense dictates that strenuous activity be avoided for several days. The patient is instructed to notify the physician of persistent uterine cramping, bleeding or leakage of amniotic fluid from the vagina, or fever.[1]

Amniocentesis can usually be done in cases of multiple gestations[1,3,4]; separate sacs must exist for each fetus, and each must contain adequate amniotic fluid. After fluid is aspirated from the first sac, 2 to 3 ml of indigo carmine (diluted 1:10 in bacteriostatic water) is injected before the needle is withdrawn. A second amniocentesis is then done, with a fresh needle insertion site chosen to direct the needle into the second amniotic sac. The aspiration of clear amniotic fluid confirms that the second sac has been entered. An experienced physician can successfully perform twin amniocenteses in 95% of cases, with ostensibly no more procedure-related risks than in single pregnancies; of course, risks for fetal morbidity and mortality are greater in multiple gestations than in single pregnancies. Each additional fetus can be evaluated similarly by injecting indigo carmine solution into successive amniotic sacs.

TABLE 1.—*Indications for Offering Invasive Prenatal Diagnosis*

Increased risk for fetal chromosome abnormalities
Advanced maternal age (≥35 yrs at time of delivery)
Previous offspring with chromosome abnormality
Parental chromosome abnormality
Balanced parental chromosome rearrangement
Miscarriages (3 or more)
Fetal structural defects (cystic hygroma)
Increased risk for mendelian disorders detectable by molecular biologic techniques (sickle cell anemia, cystic fibrosis)
Increased risk for mendelian disorders detectable by enzyme assays (Tay-Sachs disease)
Increased risk for polygenic or multifactorial conditions detectable by amniotic fluid analyses (neural tube defects, anterior abdominal wall defects)

Figure 1.—In an ultrasonogram of an amniocentesis done at 15.1 weeks' gestation, the needle tip is visualized within the amniotic cavity (from Shulman et al[1]).

Safety

The safety of genetic amniocentesis has been addressed by several large collaborative studies. The original trial was sponsored by the National Institute of Child Health and Development[5]; of 1,040 women undergoing amniocentesis, 3.5% experienced fetal loss after amniocentesis compared with 3.2% of concurrent controls (992 patients). This small difference was not statistically significant. In the United Kingdom, a collaborative trial revealed that the loss rate after amniocentesis was significantly higher than in controls (2.6% for the amniocentesis group compared with 1% for controls).[6] A common indication for amniocentesis in the United Kingdom group, however, was an elevated maternal serum AFP level, a factor associated with increased fetal mortality. In a later analysis, after subjects undergoing amniocentesis for that reason were excluded, the difference between subject and control groups was reduced to less than 1%. Nonetheless, this difference remained significant.

High-resolution ultrasonography was not employed in

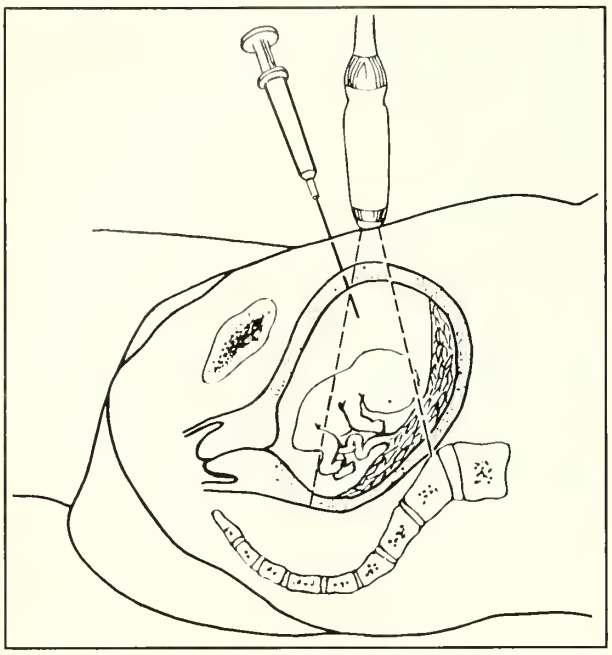

Figure 2.—The diagram illustrates the proper amniocentesis procedure (from Simpson and Elias[2]).

either the American or British collaborative trial; in fact, ultrasonography was sometimes not used at all. A possible explanation for the ostensible failure of high-quality ultrasound studies to decrease the pregnancy loss rate is that loss rates in the original US study, specifically in the control group, were spuriously high. Indeed, the reported loss rate after 16 weeks in controls (3.2%) in the US trial was actually closer to that expected at 8 to 9 weeks' gestation,[7] although variables such as differences in maternal age make precise comparisons difficult. Moreover, some obstetricians participating in the American and British studies were relatively inexperienced with the procedure. Therefore, contemporary obstetricians may assume that the actual increase in loss rate contributed by amniocentesis is less than the 0.5% usually counseled. In a prospective randomized study involving 30- to 34-year-old Danish women, however, the loss rate was 1.7% in the amniocentesis group and only 0.7% in the control group ($P < .05$).[8] The obstetricians involved were highly experienced and used high-resolution concurrent ultrasonography. Indeed, to date, no large studies have shown the increase in loss rate to be less than 0.5%. We therefore recommend counseling patients that the increased risk of fetal mortality attributable to amniocentesis may be as high as 0.5%. Finally, we counsel patients that the risks of serious maternal complications or fetal injuries are remote but do exist.

Accuracy

The analysis of amniotic fluid, as well as that of chorionic villi or fetal tissue, entails difficulties that need to be recognized by obstetricians caring for patients who undergo invasive prenatal diagnostic tests. First, cells obtained by amniocentesis may not grow, or growth may be insufficient to obtain metaphases for cytogenetic analysis. Amniotic cell cultures are usually successful; both Canadian[9] and American[10] collaborative trials comparing chorionic villus sampling (CVS) and amniocentesis revealed the failure to obtain cytogenetic results for patients undergoing amniocentesis to be uncommon (0.1% in the Canadian study and 0.9% in the American study).

Second, maternal cells may be inadvertently included in the specimen, thereby creating the possibility of an incorrect diagnosis. This source of possible error is of greater concern with CVS and percutaneous umbilical blood sampling; in theory, discarding the syringe containing the first milliliter of aspirated amniotic fluid should reduce the chance of maternal cell contamination.

A third source of error involves chromosome abnormalities that are not representative of fetal complement. Such chromosome abnormalities may arise in culture and should be suspected whenever they are restricted to only one of the several culture flasks or clones started from a single amniotic fluid specimen. In fact, cells containing at least one additional structurally normal chromosome are detected in 1% to 2% of all amniotic fluid specimens.[11,12] When such cells are confined to a single culture or clone, the phenomenon is termed pseudomosaicism; when they are found in more than one flask or clone, the phenomenon is termed true mosaicism. True mosaicism is found in 0.25% of amniotic fluid specimens, and true mosaicism is confirmed by studies of the abortus or neonate in 70% to 80% of cases.[11] Although pseudomosaicism is not associated with an increased risk for fetal morbidity or mortality, true mosaicism is associated with an increased risk of phenotypic and developmental abnormalities.

A fourth possible problem is that some phenotypes are difficult to predict from the chromosome complement. This is especially the case when an apparently balanced translocation, small inversion, or small supernumerary chromosome is identified. If one of the phenotypically normal parents has the same chromosome aberration, reassurance is generally appropriate. Apparently balanced de novo structural abnormalities, such as chromosome translocations and supernumerary chromosomes, are associated with about a 10% risk of phenotypic abnormalities.[13]

Patients must therefore be made aware that although laboratory failure and cytogenetic discrepancies are now uncommon in amniocentesis, they do occur and may lead the physician to recommend either a second amniocentesis or a different diagnostic test, such as percutaneous umbilical blood sampling, to further evaluate the fetal state.

Early Amniocentesis

The desire to provide invasive prenatal diagnosis in the first trimester of pregnancy led to the development of chorionic villus sampling, a procedure found to be both safe and reliable. Many medical centers, however, do not have the capabilities to do CVS and have begun to investigate the use of amniocentesis before 15 weeks' gestation. Also, a prenatal diagnostic procedure should be available to women presenting after the 12th gestational

week, the closing time for acceptance into most CVS programs, but before the 15th gestational week when conventional amniocentesis can be done. No set definition of early amniocentesis exists as yet; many researchers define early amniocentesis as a procedure performed before the 15th gestational week. At our institution, those procedures done before the 14th gestational week are considered "early."

Early amniocentesis is done in a manner similar to traditional amniocentesis, except that less fluid is removed, usually 1 ml for each completed week of gestation.[1] Some authors have described difficulty in obtaining the amniotic fluid specimen at less than 13 weeks' gestation; this presumably results from membrane tenting, the chance of which is greater before 14 weeks' gestation.

Data from several studies suggest that early amniocentesis is a promising technique for first-trimester prenatal diagnosis. Benacerraf and colleagues reported on 100 consecutive patients undergoing amniocentesis between 11 and 14 weeks' gestation.[14] Among 94 pregnancies allowed to continue, "all . . . were progressing normally at follow-up, which occurred at delivery or 1 month or more after the procedure."[14(p710)] Nevin and associates reported on 222 early amniocenteses; 60% were done at 14 weeks' gestation, 27% at 13 weeks, and 11% at 12 weeks.[15] The postprocedure abortion rate was 1.4%. Penso and Frigoletto reported on 407 women undergoing amniocentesis between 11 and 14 weeks and found a loss rate within four weeks of the procedure to be 2.3%, with another 1.6% loss thereafter.[16] In 1992 Hanson and co-workers reported a total postprocedural loss rate of 3.4% among 936 women undergoing amniocentesis at 12.8 weeks' gestation or earlier.[17] In the same year, Henry and Miller presented information on 1,805 early amniocenteses, 35% of which were done at 14 weeks' gestation or earlier.[18] The total loss rate in this study was 0.6%; the loss rate in procedures performed between 14.0 and 14.9 weeks was similar to the loss rate in procedures performed earlier than 14.0 weeks.

These reports suggest an increasing use of early amniocentesis for prenatal diagnosis. Moreover, the impression among some obstetricians is that early amniocentesis involves no special techniques or concerns about safety or accuracy. Henry and associates in their report of 55 cases declared that early amniocentesis "requires no new techniques in counseling, clinical procedure or laboratory analysis."[19(pA219)] Sandstrom and colleagues wrote that "early amniocentesis is an alternative method of prenatal diagnosis."[20(pA385)] Burton and co-workers described a 68% increase in early specimens received by their laboratory after informing local obstetricians of the availability of the laboratory analysis and the usefulness of this service[21]; several reference laboratories and prenatal diagnostic services now advertise early amniocentesis in commercial brochures. Early amniocentesis apparently is being offered as a routine prenatal diagnostic test, with patients being informed that the safety and accuracy of the procedure are equivalent to those of traditional amniocentesis.

We do not think reported data as yet bear out the contention that early and conventional amniocentesis are equal in safety and accuracy. Fetal loss rates following early amniocentesis and the reliability of the procedure need to be evaluated more rigorously. Most reports and abstracts provide estimates of fetal loss rates based only on pregnancies in progress, with little reference to a delivered cohort of patients. A report by Dunn and Godmilow[22] was especially instructive in this regard because initially they were advocates of early amniocentesis.[23,24] In their series, the loss rate before 28 weeks' gestation was 1.9% after CVS, 4.2% after early amniocentesis, and 1.1% after traditional amniocentesis ($P < .001$). Burton and associates[21] and Crandall and colleagues[25] have reported diagnostic discrepancies between certain tests done on amniotic fluid specimens obtained in the first and early second trimesters. In addition, Wathen and co-workers found that the rapidly changing levels of AFP from 8 to 10 weeks' gestation made such analyses impracticable for prenatal diagnosis.[26] Further studies are needed to assess the efficacy of AFP, AChE, and other biochemical marker studies in amniotic fluid specimens obtained from early amniocentesis procedures. Overall, early amniocentesis cannot yet be assumed to be as safe or effective as traditional amniocentesis, although initial data suggest it may eventually be proved as safe and reliable as conventional amniocentesis or CVS.

Chorionic Villus Sampling

Second-trimester amniocentesis has traditionally been the most common invasive technique for the prenatal diagnosis of genetic disorders. A safe and reliable test for first-trimester prenatal diagnosis has long been sought. Such a technique would be desirable for several reasons. Patient privacy would be protected because testing would be done at a stage when ostensible signs of pregnancy are few. First-trimester prenatal diagnosis would permit a woman who has been diagnosed as carrying a fetus with an abnormality to undergo first-trimester pregnancy termination, a procedure associated with low morbidity and substantial psychological benefit. Early diagnosis may be necessary for fetal treatment, as is demonstrated by the prevention of female pseudohermaphroditism in the treatment of fetal 21-hydroxylase deficiency with dexamethasone administered to the mother.

Chorionic villus sampling is now recognized as a safe and reliable method for first-trimester prenatal diagnosis. In this section we review techniques, safety, and efficacy of first-trimester CVS and the increasing use of the technique for prenatal diagnosis later in pregnancy.

Technique

Chorionic villus sampling for first-trimester prenatal diagnosis is usually done between 9.5 and 12.5 weeks' gestation. The indications for this procedure are essentially the same as those for amniocentesis, except that some fetal abnormalities, such as neural tube defects and anterior abdominal wall defects, are amenable to prenatal diagnosis only by analysis of amniotic fluid; patients at

increased risk for such abnormalities are not candidates for CVS (Table 1).

As with amniocentesis, a complete counseling session should precede the sampling procedure. In addition, a detailed ultrasound examination should be done before sampling to assess fetal viability, number, and gestational age and placental location. Also necessary are results of an indirect Coombs' test and determination of the patient's ABO and Rh status. Maternal sensitization is a relative contraindication to CVS, and all Rh-negative women whose partners are Rh positive or who are unaware of their blood type should receive Rh immune globulin after the sampling procedure.

The selection of an appropriate approach is based primarily on placental location, but certain conditions may preclude a given approach. For example, uterine leiomyomata or intervening intra-abdominal structures, such as the small bowel, may preclude transabdominal CVS, whereas active cervicovaginal disease, such as herpes or chronic cervicitis, may preclude transcervical and transvaginal approaches. At our institution, this technique is offered to women with multiple gestations only if placentas are clearly separate and individually accessible.

After sampling, fetal heart activity is verified by ultrasonography and all patients are monitored for any untoward effects for about 30 minutes. Rh immune globulin (300 μg at our institution) is administered to appropriate patients, and all patients are encouraged to consider maternal serum AFP screening at 15 to 20 weeks' gestation.[1]

Transcervical approach. For transcervical CVS, patients are placed in the lithotomy position. After a speculum is placed, the vagina is cleansed with an iodine-based solution. Under continuous ultrasound guidance, a plastic catheter with an inner, malleable metal obturator (Figure 3) is introduced transcervically into the placenta (Figure 4). The optimal catheter placement is along the long axis of the placenta and away from the gestational sac and myometrium. Once the catheter is properly placed, the obturator is removed and the hub of the catheter is attached to a 20- or 30-ml syringe (Figure 5) that contains 4 to 5 ml of cytogenetic transport medium.[2]

Chorionic villi are obtained by 10 to 15 rapid aspirations of the syringe plunger to 20 or 30 ml negative pressure. The visualization of blood slowly moving up the catheter is an indication of successful sampling. When the procedure is complete, the catheter is removed under continuous negative pressure. An adequate specimen is approximately 5 to 8 mg, with optimal specimens weighing 15 to 25 mg.[1]

Transabdominal approach. For transabdominal CVS, the patient is placed in the supine position. An appropriate needle insertion site is selected during ultrasonographic examination before the procedure; in addition, close attention must be given to the location of the small bowel, which should always be avoided. Once a site is selected, the overlying skin is infiltrated with 5 ml of 1% lidocaine solution and then cleansed with an iodine-based solution.

A 19-gauge spinal needle is inserted through the maternal abdominal and uterine wall and into the placenta under continuous ultrasound guidance. The needle tip is then guided into the long axis of the placenta (Figure 6). Once the needle tip is in place, the stylet is withdrawn and a 20- or 30-ml syringe with 4 to 5 ml of transport medium is attached to the needle hub. Transabdominal aspiration is performed with the syringe attached to an aspiration device (Figure 7) to facilitate villus aspiration.[27] Chorionic villi are obtained in a manner similar to transcervical sampling, although the needle tip can be redirected within the placenta to obtain specimens from various sites and

Figure 3.—An aspiration catheter is used for transcervical chorionic villus sampling (from Shulman et al[1]).

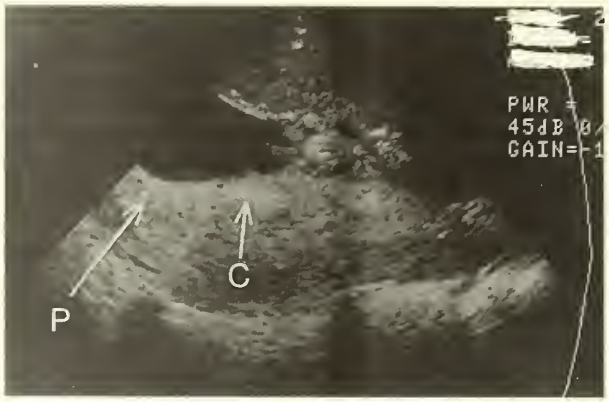

Figure 4.—An ultrasonogram shows transcervical chorionic villus sampling. The catheter (C) is within the placenta (P).

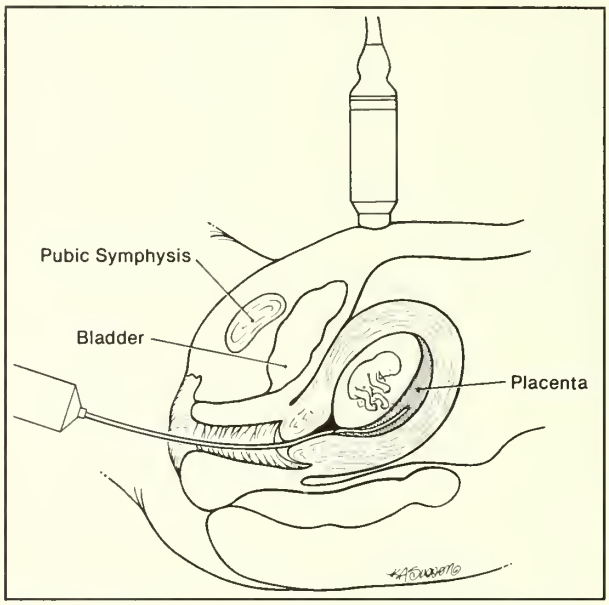

Figure 5.—The transcervical chorionic villus sampling procedure is illustrated (from Simpson and Elias[2]).

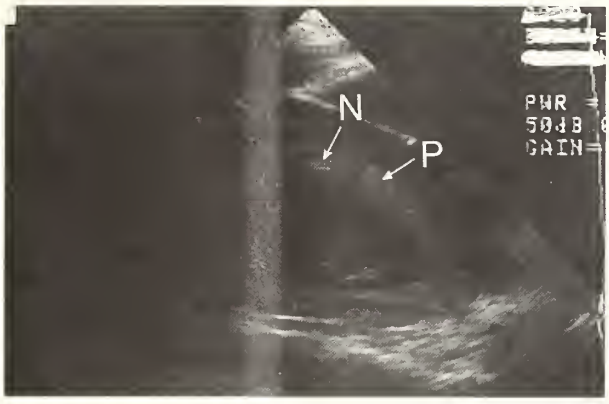

Figure 6.—In this ultrasonogram of transabdominal chorionic villus sampling, the needle tip (**N**) is within the placenta (**P**).

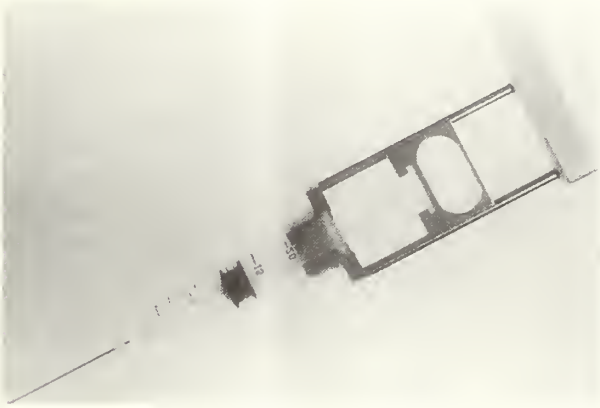

Figure 7.—An aspiration device is used to facilitate chorionic villus aspiration for transabdominal sampling (from Elias et al[27]).

further facilitate aspiration (Figure 8). Optimal specimens usually weigh 10 to 20 mg.[1]

Transvaginal approach. Transvaginal sampling is usually reserved for women presenting with a retroverted, retroflexed uterus with a posterior or fundal-implanted placenta. In this situation, neither the transcervical nor the transabdominal technique is possible. Patients are prepared in a manner similar to that for transcervical CVS. After the vagina is cleansed with an iodine-based solution, the posterior wall of the vagina is anesthetized with 2 to 5 ml of a 1% lidocaine solution. During the placement of lidocaine, transabdominal ultrasonography is used to follow the needle tip within the vaginal mucosa and assess whether continuous visualization of the aspiration needle is feasible (Figure 9). If not, transvaginal CVS using endovaginal guidance may be considered, or prenatal diagnosis may be deferred until the second trimester. At our center, transvaginal sampling is offered to about 4% of women desiring first-trimester CVS; less than 1% of women who desire some form of CVS are unable to undergo the procedure because of technical considerations.

We use a 35-cm, 18-gauge aspiration needle to obtain chorionic villi; the needle is inserted through the posterior vaginal mucosa and uterine wall and into the placenta under continuous ultrasound guidance (Figure 10).[28] Once the needle tip is in the placenta, the stylet is removed and a 20- or 30-ml syringe containing 4 ml of transport medium is attached. Aspiration is performed in a manner similar to that for transcervical CVS. Optimal specimens weigh 10 to 20 mg.[28] As the safety of transvaginal CVS has not yet been determined, the procedure should not be performed merely in lieu of transcervical or transabdominal sampling.

Safety

Canadian and American multicenter collaborative studies initially reported pregnancy loss rates among women undergoing transcervical CVS to be 0.6% and 0.8% higher, respectively, than among women undergoing second-trimester amniocentesis.[9,10] In neither study were the increased loss rates statistically significant. The Canadian study was randomized whereas the American study involved women who chose either amniocentesis or CVS. In addition, neither study showed a significantly increased incidence of obstetric complications (intrauterine growth retardation, hypertension, abruptio placentae, or premature delivery) among women undergoing transcervical sampling.

Transabdominal and transcervical CVS also appear

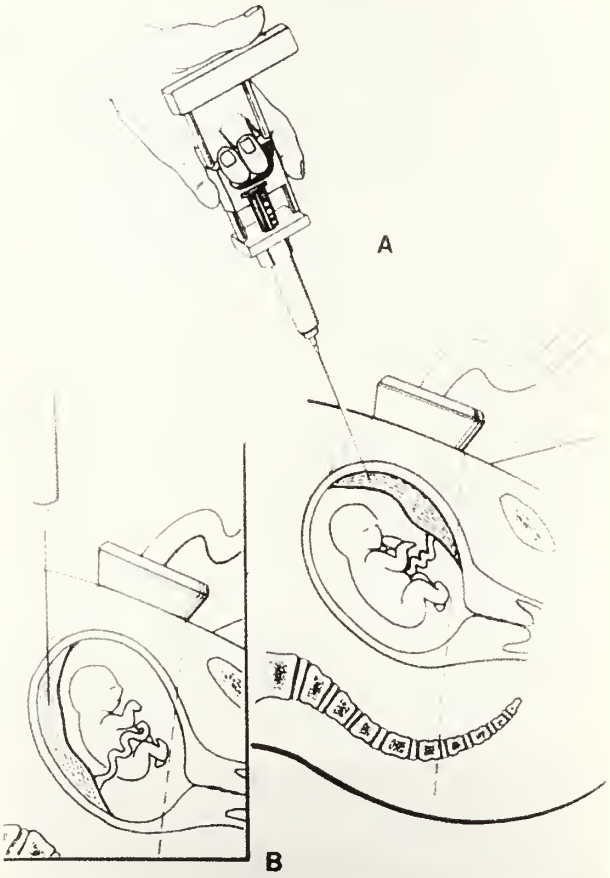

Figure 8.—The drawing shows the transabdominal chorionic villus sampling procedure. **A**, An anterior placenta is sampled. **B**, Sampling is done on a posterior placenta (from Elias et al[27]).

Figure 9.—An ultrasonogram shows a transvaginal insertion of the needle (**arrowhead**) into the placenta.

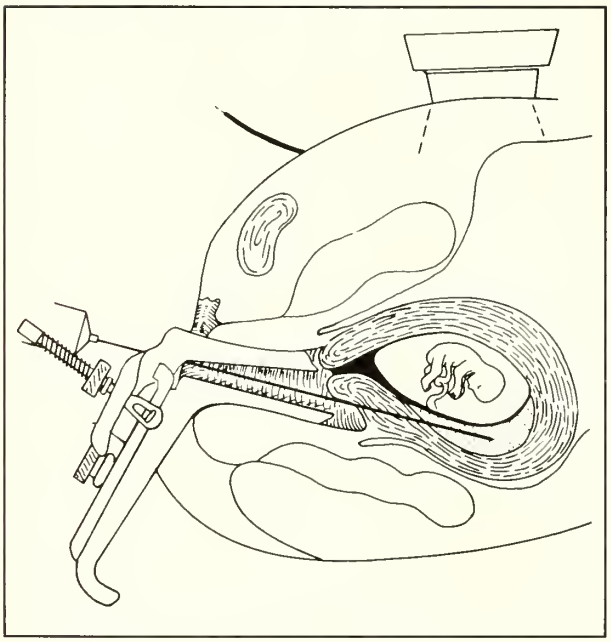

Figure 10.—The transvaginal chorionic villus sampling procedure is shown, using transabdominal ultrasound guidance (from Shulman et al[28]).

equal in safety. In a collaborative study by the National Institute of Child Health and Development, nearly 4,000 subjects were divided randomly into transcervical and transabdominal groups.[29] Loss rates through 28 weeks after the procedure among women found to be carrying euploid fetuses were 2.5% in the transcervical group and 2.3% in the transabdominal group; this difference was not statistically significant. Brambati and associates also found no differences between transcervical and transabdominal CVS in an Italian randomized trial.[30]

The one major study at odds with these results is that of the Medical Research Council, located primarily in the United Kingdom but including other European centers.[31] The measured outcome was completed pregnancies among women undergoing second-trimester amniocentesis and CVS. The finding of 4.4% fewer completed pregnancies in the CVS group was attributed to both more unintended losses and more intended terminations after the detection of fetal cytogenetic abnormalities. The latter finding appears to reflect some inexperience with cytogenetic interpretation of chorionic villi (for example, confined placental mosaicism); the former is more difficult to assess. The experience of the physicians was considerably less than for those participating in the Canadian and American trials; the only prerequisite for participation was the performance of 30 "practice" procedures. Such inexperience may thus have contributed to an increased loss rate among women undergoing CVS in the Medical Research Council trial.

Limb Reduction Defects

Concern has arisen recently about the possible association between limb defects and the sampling procedure. Limb defects involve tissue loss from at least one of the four limbs and are usually divided into two types. Longitudinal defects refer to an interruption along one of the embryologic rays of the hands, arms, feet, or legs. Transverse defects interrupt more than one of the developmental rays of the limbs, frequently resulting in an amputation-like anomaly.

Two centers have reported clusters of limb anomalies in infants whose mothers underwent CVS. Firth and colleagues reported the cases of five infants with transverse terminal limb defects among 289 cases of transabdominal sampling performed between 56 and 66 days' gestation.[32] Burton and colleagues reported the cases of four infants with transverse terminal limb defects among 436 women undergoing both transcervical and transabdominal procedures between 9.5 and 11.5 weeks' gestation.[33]

Although the report of clusters of newborn limb defects in relatively small series of women undergoing CVS is of concern, Jackson of Jefferson Medical College (Philadelphia, Pennsylvania) recently reported that 40 infants with limb reduction defects have been identified among more than 80,000 cases in a multicenter CVS registry, for an incidence of approximately 6 limb defects per 10,000 sampling cases.[34] Froster-Iskenius and Baird have reported a similar incidence of limb defects among all neonates in their analysis of birth registry data from British Columbia.[35] Accordingly, World Health Organization researchers concluded that there is little evidence to suggest a substantive risk of congenital malformations when CVS is performed after the eighth completed gestational week.[34] Chorionic villus sampling should probably not be done routinely before 9.0 weeks' gestation, however, as evidenced by the experience of Brambati from Milan, Italy. Analysis of data from Brambati's highly experienced center demonstrated a small cluster of newborns with limb-reduction defects in cases of very early CVS (7 to 8 weeks' gestation), but no such cluster with cases of traditional sampling (9 to 12 weeks' gestation).[34]

Determining whether the procedure is associated with fetal limb defects will not be an easy task. Many issues serve to preclude a simple statistical analysis, such as gestational age at time of sampling, CVS approach, physi-

cian experience, diagnostic equipment, types of associated limb defects, the interaction of mendelian or polygenic-multifactorial disorders, possible mechanisms of resulting limb defects, and the possible association of other structural defects such as hypoglossia or hypodactylia syndrome. Women considering the procedure should be informed of its possible association with limb defects and of the availability of traditional amniocentesis as an alternative procedure. At the same time, the preponderance of current data does not demonstrate a genuine association between fetal limb reduction and CVS performed by experienced personnel at or after 9 weeks' gestation.

Accuracy

Physicians who care for women undergoing CVS should be aware of the problems associated with the analysis of chorionic villi. Chorionic villi consist of two cell types: cytotrophoblastic cells, which are rapidly dividing cells that are used for direct metaphase analyses, and mesenchymal core cells that are used to initiate cell cultures. Cytotrophoblasts can be directly analyzed within 72 hours, whereas the analysis of mesenchymal core cells requires culture stimulation that usually results in metaphases suitable for cytogenetic analysis in seven to ten days. Both cell types offer advantages and drawbacks for prenatal cytogenetic analysis. Although the direct analysis of cytotrophoblasts can provide rapid results (usually within 24 to 72 hours), the quality of metaphases obtained is usually less than that obtained by culture. Conversely, the culture of mesenchymal core cells provides a better-quality metaphase spread for cytogenetic analysis, although including maternal decidua in the cell culture could lead to an incorrect cytogenetic analysis as a result of maternal cell contamination.

Several obvious problems are associated with the analysis of chorionic villus cells: Cells may not grow, growth may be insufficient for adequate analysis, or rapidly dividing cells may not respond to the laboratory techniques required for metaphase analysis. Fortunately, the combination of cell culture failure and the failure to obtain direct results is uncommon. Maternal cell contamination may lead to an erroneous cytogenetic analysis; the concurrent analysis of uncultured cytotrophoblastic cells and cultured mesenchymal core cells decreases the chance that maternal cell contamination of cultured cells will lead to a discrepant analysis. Careful examination of the chorionic villus specimen under a dissecting microscope also allows chorionic villi to be distinguished from decidua, further decreasing the chance of maternal cell contamination.

Also of concern is the possibility that chromosome abnormalities in chorionic villi do not represent the fetal chromosome complement or, conversely, that a euploid cytogenetic result from CVS does not represent an aneuploid fetal complement. In the US Collaborative Study on CVS, cytogenetic diagnosis (direct, by culture, or both) was achieved in 99.7% of 11,473 cases in which chorionic villi were obtained.[36] No incorrect diagnoses involving trisomies 21, 18, or 13 were reported. Thirteen unusual aneuploidies (0.11%)—tetraploidy (4 cases) and trisomies of chromosomes 7 (2 cases), 3, 8, 11, 15, 16, 20, and 22—were observed in the direct or culture method, but none by amniotic fluid or fetal tissue cell culture. Mosaic cytogenetic abnormalities were observed with equal frequency in direct and culture preparations in 0.8% of the 11,473 cases but were confirmed as fetal mosaicism more frequently when detected by culture methods rather than direct analyses. Only one incorrect sex prediction was observed in this large series, a 46,XY infant born to a mother whose CVS demonstrated a 46,XX complement; only analysis of cultured chorionic villi was available.

Discrepancies may thus arise between cultured mesenchymal core cells and directly prepared cytotrophoblastic cells. Analysis of the data reported by Ledbetter and co-workers shows the culture method to have a higher degree of diagnostic accuracy than direct analyses, although neither technique is completely reliable.[36] Mosaicism in direct analyses is especially likely not to be confirmed in cultures of mesenchymal core cell or fetal tissue, although recent evidence indicates that such pregnancies may still be at increased risk for an adverse perinatal outcome. The proportion of cases in which direct analyses provide ambiguous cytogenetic results is low (approximately 1%), and most of these ambiguities are resolved by the analysis of cultured mesenchymal core cells. Nonetheless, the direct method can be a useful adjunct to the culture method, in which maternal cell contamination can lead to incorrect sex prediction and, potentially, false-negative diagnostic results.

Despite these caveats, a definitive diagnosis is obtained in almost all cases; only occasionally is amniocentesis required to clarify ambiguous CVS results. Overall, CVS accuracy is comparable to that of amniocentesis, but additional tests (such as amniocentesis) should be considered before acting on nonmosaic rare trisomies and, as in amniotic fluid analyses, polyploidies.

Late Chorionic Villus Sampling

Chorionic villus sampling has also been used for prenatal diagnosis in the second and third trimesters. In most cases, CVS is offered to evaluate fetuses with structural defects in which a more rapid cytogenetic analysis is required for pregnancy management than can be obtained by amniocentesis. Sampling after 12 weeks' gestation is restricted to the transabdominal approach; early experience suggested that the transcervical loss rate was unacceptably high after 12 weeks.

Although late CVS is performed in a manner similar to that for the first-trimester transabdominal procedure, we have found that the aspiration of chorionic villi from second- and third-trimester placentas is somewhat more difficult than aspiration from first-trimester placentas. Accordingly, a more rigorous aspiration technique using an 18-gauge needle is required to obtain suitable specimens.

Diagnostic problems, such as placental mosaicism, encountered in the analysis of chorionic villi obtained

from first-trimester placentas have been encountered in the second and third trimesters as well. We found no diagnostic errors in a small group of 57 chorionic villus samples obtained during the second and third trimesters,[37] and Basaran and colleagues reported no diagnostic errors among 53 specimens evaluated.[38] In addition, Holzgreve and associates reported no immediate or late complications among 73 women undergoing procedures at between 15 and 37 weeks' gestation.[39] Further investigation will be required to determine the safety and efficacy of late sampling.

Late CVS should be considered as an alternative prenatal diagnostic test to percutaneous umbilical blood sampling. At times, it may be the only procedure available to provide prenatal information regarding fetal chromosome complement, as in some cases of oligohydramnios. Although many perinatologists in the United States primarily use umbilical blood sampling rather than late CVS for rapid karyotypic analysis in the second and third trimesters, the choice is less clear-cut elsewhere in the world. Late CVS deserves consideration as an alternative diagnostic procedure for detecting fetal chromosome abnormalities.

Use and Cost of Prenatal Diagnosis

Amniocentesis and chorionic villus sampling are used primarily by two groups of women: those who are 35 years of age or older at their estimated date of delivery and those who have been found to be at increased risk for fetal neural tube defects or the Down syndrome as a result of maternal serum analyte screening. This screening is performed during the second trimester; accordingly, only amniocentesis is an option for those women who elect invasive prenatal testing after receiving an abnormal screening result. Amniocentesis is available throughout the United States and is performed by many obstetrician-gynecologists and by some family practitioners who provide obstetric services. Conversely, CVS is available at a few centers throughout the United States and is, for the most part, done by a select group of obstetricians with special training in genetics, maternal-fetal medicine, or both. Costs for amniocentesis and CVS vary by geographic location, laboratory, and the specific tests done; however, most insurance plans that cover obstetric services provide reimbursement for either test if the patient is at increased risk for a detectable fetal abnormality.

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Fetal Tissue Sampling—Indications, Techniques, Complications, and Experience With Sampling of Fetal Skin, Liver, and Muscle

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Invasive prenatal testing has become an important way to evaluate fetuses at increased risk for hereditary disorders. In utero sampling of fetal skin, liver, and muscle may be required to diagnose before-birth disorders that cannot be diagnosed by analysis using chorionic villi or amniotic fluid. In the next few years, many of these conditions will be detected by DNA analysis, and the need for these procedures may decrease dramatically. First performed by fetoscopy, fetal tissue sampling is now most frequently done by inserting a biopsy needle under continuous ultrasonographic guidance. We describe the indications, techniques, complications, and experience with obtaining fetal skin, liver, and muscle biopsy specimens.

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In utero sampling of fetal skin, liver, and muscle has become an important method to evaluate fetuses at increased risk for congenital abnormalities. In the past, certain genetic disorders—such as X-linked hypohidrotic ectodermal dysplasia, ornithine transcarbamylase deficiency, carbamoyl-phosphate synthetase deficiency, and nonketotic hyperglycinemia—could be diagnosed using only invasive fetal biopsy techniques. Some of these can now be diagnosed rapidly by enzyme assay or by DNA analysis using amniotic fluid cells or chorionic villi.[1-5] When meiotic recombination occurs or the results of DNA analysis are uninformative, the direct examination of fetal skin, liver, or muscle may provide the only means of prenatal diagnosis.

Fetal Skin Sampling

Genodermatoses are severe and often fatal hereditary skin disorders. Fetal skin sampling is the only method available to diagnose many of these conditions before birth. Fetal skin biopsy was first performed by fetoscopy[6-9]; it is now frequently done by percutaneously inserting a biopsy forceps under continuous ultrasonographic guidance.[10] The first reports on successful prenatal diagnosis by light and electron microscopy of fetal skin biopsies concerned fetuses at risk for bullous congenital ichthyosiform erythroderma,[11] harlequin ichthyosis,[12] and the Herlitz syndrome, epidermolysis bullosa letalis.[13] Over the past ten years, more than 200 cases of prenatal diagnosis by fetal skin sampling have been reported (Table 1).[11-34] Between January 1979 and July 1992, fetal skin sampling was carried out for prenatal diagnosis in 23 women at the University of California, San Francisco (UCSF).[35] Satisfactory specimens were obtained in 22 cases. Of the 23 women, 5 had preterm deliveries. Another had a spontaneous abortion associated with chorioamnionitis two days after the sampling procedure. One woman was still pregnant at the time this was written. The prenatal diagnosis was confirmed after delivery or termination in 18 cases. In one case in which sampling was done to evaluate for ichthyosiform erythroderma, although the results of the sampling were normal, the infant was found to be mildly affected after delivery. Three women were lost to follow-up.

Indications

Genodermatoses that require fetal skin specimens for prenatal diagnosis are those disorders not diagnosable by analysis using chorionic villi or amniotic fluid components. Table 1 provides a list of genodermatoses that have been prenatally diagnosed using fetal skin specimens.

In the future, some of the conditions listed in Table 1 will be detected by DNA analysis and thereby diagnosed by either chorionic villus sampling or amniocentesis. Fetal skin sampling would be required only if the results of the DNA analysis were uninformative.

Technique

Before any fetal skin sampling procedure, the mother undergoes a preliminary ultrasonographic examination to confirm gestational age, determine fetal viability, diag-

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TABLE 1.—*Prenatally Detectable Genodermatoses by Fetal Skin Sampling*

Disorder	*Inheritance*	*Source*
Anhidrotic ectodermal dysplasia	Autosomal recessive	Arnold et al, 1984[14]
Bullous congenital ichthyosiform erythroderma (epidermolytic hyperkeratosis)	Autosomal dominant	Golbus et al, 1980[11]; Anton-Lamprecht, 1983[15]; Eady et al, 1986[16]; Jurkovic and Kurjak, 1989[17]
Nonbullous ichthyosiform erythroderma	Autosomal recessive	Perry et al, 1987[18]
Epidermolysis bullosa dystrophica (Hallopeau-Siemens)	Autosomal recessive	Anton-Lamprecht et al, 1981[19]; Bauer et al, 1986[20]; Nazzaro et al, 1989[21]
Epidermolysis bullosa letalis (Herlitz)	Autosomal recessive	Rodeck et al, 1980[13]; Heagerty et al, 1987[22]; Bakharev et al, 1989[23]; Aïvazian et al, 1990[24]; Shimizu et al, 1991[25]
Harlequin ichthyosis	Autosomal recessive	Elias et al, 1980[12]; Blanchet-Bardon et al, 1983[26]; Blanchet-Bardon and Dumez, 1984[27]; Blanchet-Bardon et al, 1989[28]; Suzumori and Kanzaki, 1991[29]
Hypohidrotic ectodermal dysplasia*	X-linked recessive	Gilgenkrantz et al, 1989[30]
Oculocutaneous albinism	Autosomal recessive	Eady et al, 1983[31]; Rosenmann et al, 1991[32]
Sjögren-Larsson syndrome	Autosomal recessive	Kousseff et al, 1982[33]; Trepeta et al, 1984[34]

*Fetal skin sampling is done only when a DNA analysis is uninformative.

nose multiple pregnancy, diagnose fetal structural abnormalities, determine the fetal lie, and locate the placenta. Fetal skin sampling is optimally done between 17 and 20 weeks' gestation, depending on the indication.

The patient is usually premedicated with 5 to 10 mg of intravenous diazepam (Valium). The abdomen is prepared with an iodine-based solution and alcohol and draped in a sterile manner. The skin is infiltrated with a 1% lidocaine hydrochloride solution for local anesthesia. A trocar is then introduced into the uterus, and a biopsy forceps is passed through the cannula to obtain approximately 2 mm of skin, preferably the thorax, back, buttocks, or, for certain diagnoses (oculocutaneous albinism), the scalp. The entire procedure is done under continuous ultrasonographic guidance. An ultrasound examination is performed immediately after the procedure to assess fetal viability. After sampling, the specimen is placed in appropriate fixative for electron and light microscopy. The methods to evaluate fetal skin for various prenatal diagnoses have been well described.[7,8,11-13,19,36-40]

Complications

In experienced centers, the incidence of fetal loss from fetoscopy and fetal skin biopsy is not more than 5%.[41] Principal risks include spontaneous abortion, the leakage of amniotic fluid, infection, premature labor and delivery, hemorrhage from injury to the anterior abdominal wall, uterus, or placenta, maternal and fetal injuries, and cosmetic or functional injuries. To date, there have been too few fetal skin sampling procedures done by ultrasound-guided skin biopsy to draw any conclusions about safety compared with fetoscopy.

Fetal Liver Biopsy

Most inborn errors of metabolism can be diagnosed by analysis using amniotic fluid or chorionic villi; some liver enzyme abnormalities are not currently diagnosable by DNA analysis, however. Fetal liver biopsy becomes the only method available to diagnose these conditions before birth. The first reports on successful prenatal diagnosis by fetal liver biopsy concerned pregnancies at risk for ornithine transcarbamylase deficiency.[42,43] Over the past ten years, 11 cases of the use of fetal liver biopsy have been reported.[35,42-46] During this period, 16 fetal liver biopsies were done at UCSF,[35] and satisfactory specimens were obtained in all but 1 case. There were no spontaneous abortions or preterm deliveries. All diagnoses were confirmed after delivery or the termination of pregnancy. One woman was lost to follow-up.

Indications

Indications for fetal liver biopsy include fetuses at risk for ornithine transcarbamylase deficiency,[42,43] carbamoyl-phosphate synthetase deficiency,[45,46] or von Gierke glycogen storage disease, type IA.[44] Recent advances in DNA technology have identified mutations in the ornithine transcarbamylase gene[3,4,47] and the carbamoyl-phosphate synthetase gene,[48] permitting prenatal diagnosis to be made by DNA analysis of amniotic fluid cells or chorionic villi. Fetal liver biopsy is still needed for those cases in which DNA analysis is not informative for the detected mutations.

Technique

Similar to fetal skin sampling, fetal liver biopsy requires a preliminary ultrasonographic examination. The procedure is performed optimally between 17 and 20 weeks' gestation. If needed, the patient is premedicated with 5 to 10 mg of intravenous diazepam, and a 1% lidocaine solution is given for local anesthesia. A 16.5-gauge thin-walled needle is introduced into the amniotic cavity under continuous ultrasonographic guidance. The biopsy needle is then directed below the right costal margin and into the fetal liver. Once the needle is in the liver parenchyma, a syringe is attached to aspirate fetal liver into the biopsy needle. The tissue is removed from the needle by flushing with saline solution.[35] The specimen is then processed for appropriate enzyme assays.[42-46] An ultrasound examination is done immediately after the procedure to assess fetal status.

Complications

Complications that can possibly arise from fetal liver biopsy are similar to those described with fetal skin sampling. Too few fetal liver biopsies have been done to assess a meaningful complication rate for the procedure.

Fetal Muscle Biopsy

Indications

Duchenne-type muscular dystrophy is a progressive, degenerative muscle disease that is inherited as an X-linked recessive trait. Prenatal diagnosis and carrier detection for this disorder can usually be done using DNA analysis. When recombination occurs within the gene for Duchenne muscular dystrophy, DNA analysis is uninformative, or carrier status cannot be ascertained, fetal muscle biopsy with dystrophin analysis may provide the only means of prenatal diagnosis. The first successful prenatal diagnosis by dystrophin analysis of fetal muscle biopsy was performed in 1991.[49] Fetal muscle biopsy was recently used for prenatal diagnosis in three pregnant women at UCSF.[50] Two other fetal muscle biopsies were also done by the UCSF staff. In the last two cases, satisfactory specimens were obtained, and immunofluorescence studies verified the presence of normal dystrophin in both. Unfortunately, one pregnancy resulted in spontaneous abortion three weeks after the sampling, but the other resulted in the term delivery of a normal male infant.

Technique

After a preliminary ultrasonographic examination, the woman is sedated to reduce fetal movement, and the skin is infiltrated with 1% lidocaine solution. Fetal muscle is obtained at 16 to 22 weeks' gestation by directing a 14-gauge (Tru-Cut) biopsy needle through the maternal abdomen and obliquely into the fetal gluteal region (Figure 1). Real-time ultrasonography is used for continuous visualization. After sampling, the specimens are verified for the presence of muscle fibers, and immunoblotting or immunofluorescence is used to determine the presence or absence of dystrophin (Figure 2).[50] An ultrasound examination is done immediately after the procedure to assess fetal status.

Figure 1.—The sonogram shows a fetus undergoing muscle biopsy. The closed arrow points to needle in a fetal buttock. The open arrows point to ischial tuberosities.

Complications

Too few fetal muscle biopsies have been performed to assess the safety of the procedure. Possible complications include spontaneous abortion, the leakage of amniotic

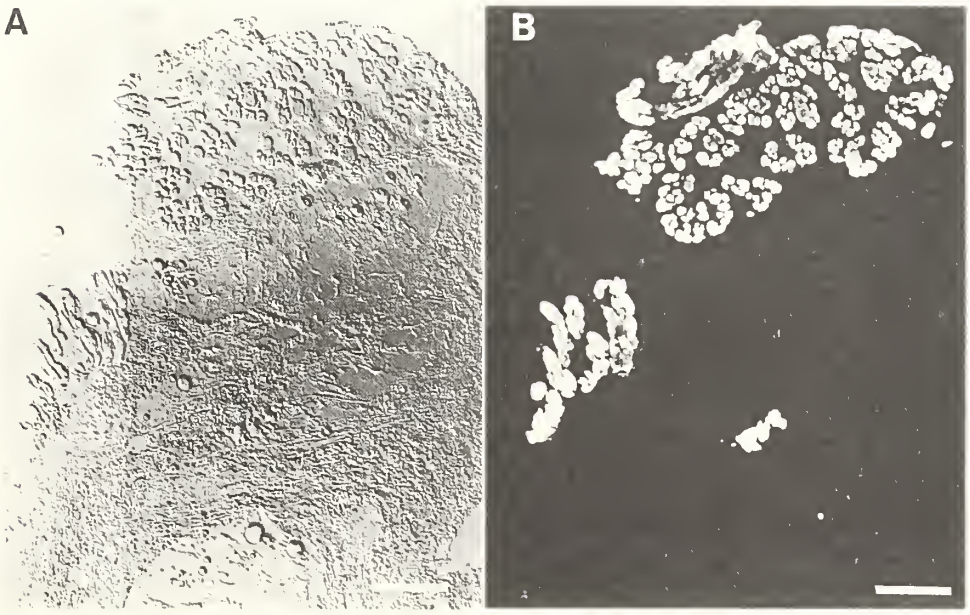

Figure 2.—The muscle fiber content is shown of a biopsy specimen using **(A)** Normarski optics and **(B)** immunofluorescence of muscle-specific myosin heavy chain protein in the same section. The muscle fibers are refractile with Normarski and stain positively for myosin. The myosin-negative tissue is epidermis and connective tissue. bar = 500 μm

fluid, fetal or maternal hemorrhage, fetal or maternal injury, infection, prematurity, and cosmetic or functional fetal injury.

Conclusion

Over the past decade, substantial advances in invasive prenatal diagnostic techniques, such as fetal skin sampling, fetal liver biopsy, and fetal muscle biopsy, have allowed the diagnosis of congenital disorders not diagnosable using amniocentesis or chorionic villus sampling. In the next few years, many of these conditions will certainly become detectable by DNA analysis, and thereby the need for these procedures may decrease dramatically. Other invasive prenatal techniques, such as fetal kidney biopsy, might become available in the near future. Ongoing animal research on fetal hematopoietic stem cell transplantation might allow fetal liver biopsy to be used for the therapeutic application of gene transfer.[51-54]

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Fetal Ultrasonography

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Since its introduction in the 1950s, ultrasonography in pregnancy has been helpful in determining gestational age, detecting multiple pregnancies, locating placentas, diagnosing fetal anomalies, evaluating fetal well-being, and guiding obstetricians with in utero treatment. We review current standards and controversies regarding the indications, safety, accuracy, and limitations of ultrasonography in pregnancy.

(Garmel SH, D'Alton ME: Fetal ultrasonography, *In* Fetal Medicine [Special Issue]. West J Med 1993; 159:273-285)

Since ultrasonography was first introduced in the late 1950s as a diagnostic tool,[1] its use has become commonplace in many obstetric practices. Advances in technology and skill have enhanced image quality and made ultrasonography the modality of choice in imaging fetuses. In the past decade, it has been used increasingly in prenatal diagnosis and treatment. Identifying an abnormal fetus allows prenatal counseling with a multidisciplinary team of experts and a discussion of pregnancy options in the face of a lethal anomaly. Furthermore, it can influence antepartum and intrapartum management, permit planning of the mode and site of delivery, and prepare the intensive care nursery for the arrival of a possibly compromised neonate, thus ensuring the best care of the fetus and newborn. Controversy exists regarding the indications and extent of its use in pregnancy, however.

With the increasing use of ultrasonography, practice guidelines have emerged. The American College of Obstetricians and Gynecologists describes two different types of ultrasound examinations—basic and targeted. A basic examination is adequate for most pregnant women and should be done by "a trained professional," although qualifications are not specified. Components of a basic examination vary by gestational age but should include the following[2]:

- Presence or absence of cardiac activity,
- Location of gestational sac and identification of fetuses (first trimester only),
- Number of fetuses,
- Evaluation of the uterus and adnexa (especially in the first trimester),
- Placental location (in the second and third trimesters),
- Amniotic fluid volume (especially in the second and third trimesters),
- Estimate of fetal age,
- Fetal presentation (in the second and third trimesters),
- Survey of fetal anatomy for gross malformations.

In contrast, a targeted examination is reserved for patients whose history, clinical findings, or the results of a basic ultrasound study put them at increased risk of carrying an abnormal fetus. The targeted examination should be done by a more experienced operator, although specific qualifications have not been delineated.

The American Institute of Ultrasound in Medicine recently approved guidelines in the hope of ensuring the performance of quality ultrasonographic examinations and the proper interpretation of these examinations.[3] These guidelines do not differentiate between basic and targeted examinations and include the evaluation of intracranial anatomy, spine, and abdomen including kidneys, urinary bladder, stomach, and cord insertion. The evaluation of the fetal anatomy may not be limited to these organ systems, and suspected defects might require further investigation with additional and perhaps more specialized studies.[4]

In 1984 members of a National Institutes of Health (NIH) Consensus Development Conference reviewed the available literature to provide guidelines for obstetrical ultrasonography.[5] Pressing issues included indications for obstetrical ultrasonography, such as routine screening versus targeted studies, and ultrasound safety. The panel suggested certain situations in which sonography might be beneficial (Table 1). Although routine screening in pregnancy is recommended in other countries, including England,[6] Norway,[7] and Canada,[8] this conference did not endorse routine ultrasonographic screening, mainly because of a lack of evidence that it benefited low-risk fetuses. Other arguments against routine screening included appreciable cost and potential fetal harm.

Theoretical safety risks addressed by the NIH confer-

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ABBREVIATIONS USED IN TEXT

AChE = acetylcholinesterase
AFP = α-fetoprotein
CNS = central nervous system
NIH = National Institutes of Health
SD = standard deviation

ence included damage from heat or cavitation from ultrasound energy. Randomized clinical trials showed no difference in developmental, neurologic, or psychological outcome,[5] with as much as 12 years of follow-up.[9] An increase in the frequency of dyslexia in screened groups compared with controls was reported. Although this did not reach statistical significance, the NIH conference recommended further study. Salvesen and co-workers compared 8- and 9-year-old children, half of whose mothers had screening sonograms while pregnant and half of whose mothers did not.[10] Teachers, blinded to in utero exposure status, were asked to assess children in terms of reading, spelling, mathematics, and overall performance skills. No differences between the two groups were found, including no difference in the frequency of dyslexia. These investigators concluded that ultrasound was safe in pregnancy.[10]

Randomized Trials Before the NIH Conference

Before the NIH conference four randomized clinical trials addressed routine sonographic screening in pregnancy. Bakketeig and colleagues screened 510 low-risk women at 19 and at 32 weeks' gestation and compared them with a control group that received only indicated scans.[11] Although none of the results were statistically significant, there was a decreased number of postdate labor inductions, a decreased number of infants who were small for gestational age, and a higher detection of twins, with a subsequent increase in gestational age and weight at delivery. None of these findings resulted in a significant difference in perinatal morbidity or mortality. Furthermore, an increase was shown in the number and duration of antepartum admissions, in part because of suspected growth retardation.

Eik-Nes and associates screened 809 women at 18 and again at 32 weeks' gestation and reported a significant decrease in postdate induction rates, with a decrease in the incidence of neonatal morbidity due to fewer pregnancies being mistakenly induced prematurely.[12] In contrast to the findings of Bakketeig and co-workers, a significant decrease in the number of antepartum hospital admissions was noted. Screened twins had a higher birth weight at delivery than those in the control group.

Wladimoroff and Laar screened 341 women once at 32 to 36 weeks' gestation.[13] A single measurement of abdominal circumference increased the detection of small-for-gestational-age and large-for-gestational-age infants. Differences in perinatal outcome were not addressed.

Bennett and co-workers screened 1,062 women once, at 16 weeks' gestation, and withheld scan results from physicians in a subset of the screened women.[14] There was an increase in induction rates for suspected growth retardation in the group with known scan results. When compared with the group without known scan results, however, there was no difference in the rates for infants small for their gestational age and no difference in perinatal mortality.

TABLE 1.—*Indications for Ultrasonography**

- Estimate gestational age for women with uncertain clinical dates or verify dates for women who are to undergo scheduled elective repeated cesarean delivery, indicated induction of labor, or other elective termination of pregnancy
- Evaluate fetal growth, for example, when the woman has an identified cause for uteroplacental insufficiency—severe preeclampsia, chronic hypertension, chronic renal disease, severe diabetes mellitus—or for other medical complications of pregnancy where fetal malnutrition (intrauterine growth retardation or macrosomia) is suspected
- Evaluate vaginal bleeding of undetermined cause
- Determine fetal presentation when the presenting part cannot be adequately determined in labor or the fetal presentation is variable in late pregnancy
- Multiple gestation suspected based on the detection of more than 1 fetal heartbeat pattern or fundal height larger than expected for dates or previous use of fertility drugs
- Adjunct to amniocentesis
- Substantial discrepancy in uterine size compared with clinical dates
- Pelvic mass detected clinically
- Hydatidiform mole suspected on the basis of clinical signs of hypertension, proteinuria, or the presence of ovarian cysts felt on pelvic examination or failure to detect fetal heart tones with a Doppler ultrasonogram after 12 weeks' gestation
- Adjunct to cervical cerclage placement
- Ectopic pregnancy suspected or pregnancy occurring after tuboplasty or previous ectopic gestation
- Follow-up evaluation of placental location for identified placenta previa
- Adjunct to special procedures, such as fetoscopy, intrauterine transfusion, shunt placement, in vitro fertilization, embryo transfer, or chorionic villus sampling
- Fetal death suspected
- Uterine abnormality suspected—clinically significant leiomyoma or congenital structural abnormalities, such as uterus bicornis or uterus didelphus
- Locate intrauterine (contraceptive) device
- Ovarian follicle development surveillance
- Biophysical evaluation for fetal well-being after 28 weeks' gestation
- Observation of intrapartum events—version or extraction of second twin, manual removal of placenta
- Polyhydramnios or oligohydramnios suspected
- Abruptio placentae suspected
- Adjunct to external version from breech to vertex presentation
- Estimate fetal weight or presentation in premature rupture of membranes or premature labor
- Abnormal serum α-fetoprotein value for clinical gestational age
- Follow-up observation of identified fetal anomaly
- History of previous congenital anomaly
- Serial evaluation of fetal growth in multiple gestation
- Evaluate fetal condition in late registrants for prenatal care

*From the National Institutes of Health Consensus Development Conference.[5]

TABLE 2.—*Randomized Clinical Trials Before and After National Institutes of Health (NIH) Consensus Development Conference*

Investigators	*Rate of Inductions*	*Detection of Twins*	*Detection of SGA Infants*	*Incidence of SGA Infants*	*No. or Length of Antepartum Admissions*	*Perinatal Morbidity or Mortality*
Before NIH Conference						
Bakketeig et al, 1984[11]	↓*	↑*	↑†	↓*	↑	No difference
Eik-Nes et al, 1984[12]	↓	↑†	↑	Unclear	↓	↓
Bennett et al, 1982[14]	↑†	Not addressed	Not addressed	No difference	Not addressed	No difference
After NIH Conference						
Neilson et al, 1984[15]	No difference	Not addressed	↑	Not addressed	Not addressed	No difference
Secher et al, 1987[16]	↑	Not addressed	↑	No difference	Not addressed	No difference
Waldenström et al, 1988[17]	↓	↑†	Not addressed	↓	No difference	↓*
Ewigman et al, 1990[18]	No difference	↑†	Not addressed	Not addressed	Not addressed	No difference
Saari-Kemppainen et al, 1990[19]	No difference	↑	Not addressed	No difference	↓*	↓‡

SGA = small for gestational age, ↑ = increased, ↓ = decreased

*Not significant. †Statistical significance is unclear. ‡Not significant if elective terminations due to malformations are counted as deaths.

These four trials were reviewed by the NIH conference, which concluded that although there were more accurate pregnancy dating and higher detection rates of twins, no improvement in pregnancy outcome was shown. The data regarding induction rates and antepartum hospital days varied among trials and was thought to be inconclusive.[5] These studies, conducted before 1984, may not be relevant today. For instance, most of these studies used only a single measurement—biparietal diameter or abdominal circumference—for dating and screened fetuses for gross anomalies only.

Randomized Trials After the NIH Conference

Five trials subsequent to the NIH conference have been reported. Neilson and colleagues noted that ultrasound study was superior to clinical examination in detecting infants small for their gestational age, but failed to show any improvement in perinatal outcome.[15] Secher and co-workers obtained a dating scan on 2,771 low-risk women before 22 weeks' gestation, then rescanned them at least twice in the third trimester.[16] Of the women felt clinically to have appropriately grown fetuses, 184 were found to have fetuses small for their age on third-trimester ultrasonography. In just more than half of these women (the treatment group), their obstetricians were informed of the sonogram results. A statistically significant increase in induction rates in this group was reported, along with a trend towards higher one-minute Apgar scores and cord pH values. No differences in gestational age at delivery, birth weight, instrumental or operative deliveries, or admissions to the neonatal ward were found.

Waldenström and associates obtained a screening scan on 2,482 women between 13 and 19 weeks' gestation and demonstrated a decrease in the number of labor inductions, a decrease in the number of small-for-gestational-age infants, and earlier detection of twin pregnancies when compared with a control group.[17] There was no difference in the number of antepartum admissions or the length of the antepartum hospital stay. Furthermore, none of these findings had an effect on perinatal mortality. Although not statistically significant, there was a decrease in perinatal morbidity, reflected by a decrease in the number of admissions to a neonatal ward.

Ewigman and co-workers studied 915 low-risk women, half of whom had routine scans, most between 10 and 12 weeks' gestation, and the other half having ultrasonograms only as clinically indicated.[18] No differences in the number of inductions, including postdate inductions, or poor perinatal outcomes, defined by low five-minute Apgar scores, prolonged neonatal intensive care unit admissions, or neonatal death, were shown. Twins were detected earlier in the group having routine sonograms, but the sample size was small, and thus the investigators concluded that there was no benefit from routine sonography.

Saari-Kemppainen and colleagues screened 4,691 women between the 16th and 20th gestational week and reported no difference in induction rates or birth weights when compared with controls.[19] A decrease in the number of antepartum hospital days in the screened group was reported, but did not reach statistical significance. Perinatal mortality was significantly decreased due to the detection of 50% of the major malformations and subsequent elective abortions.

Table 2 compares the results of these trials.[11,12,14-19] The studies are limited by small sample size and low statistical power. Although they might be able to detect differences in more common outcomes, such as antepartum hospital admissions and postdate inductions, only larger trials could prove statistical significance when looking at infrequent outcomes such as perinatal mortality.[20] In addition, the ability of these studies to detect any effect of ultrasonography is substantially diminished by the frequency of indicated scans in the control groups, generally 20% to 30%, but in Saari-Kemppainen and associates' study, it was as high as 77%.

Accuracy in Diagnosing Malformations

Congenital anomalies are responsible for 20% to 25% of perinatal deaths and an even higher percentage of perinatal morbidity.[21] Most occur sporadically in fetuses without known risk factors. For this reason, routine

sonography as a screening tool is an attractive concept. Table 3 lists fetal malformations that have been prenatally diagnosed by sonography. Some of these anomalies are more difficult to diagnose than others, whether because of technical factors such as cardiac defects, or lesion size such as small facial clefts. The detection of other anomalies, such as choroid plexus cysts, is dependent on the gestational age of the fetus.

The accuracy of sonography in detecting certain lesions prenatally is difficult to assess because of differences in the extent of the malformation(s), quality of the equipment, and the skill of the sonographer. Technical limitations—fetal position, amniotic fluid volume, or maternal habitus—will make some scans more difficult to do than others.[22(p.30)]

Studies in Low-risk Populations

Lys and co-workers retrospectively reviewed sonograms of 8,316 low-risk pregnancies and found 27 of 190 congenital malformations.[23] A sensitivity of 14%—varying from 0% with minor defects to 100% with major anomalies—and a specificity of 98% were reported. Li and colleagues examined 678 clinically uncomplicated pregnancies and detected three of eight congenital anomalies by prenatal sonograms, reporting a 38% sensitivity and a 99% specificity.[24] Levi and associates scanned 13,309 gravid low-risk women and found ultrasonography to be 34% sensitive (55% sensitive for most major defects) and 99.9% specific.[25]

Rosendahl and Kivinen examined 9,012 low-risk women with one to two sonogram examinations, depending on the year of study.[26] Despite incomplete anatomic surveys in the early years of the study, 54 of 93 abnormal fetuses were detected with prenatal sonograms, resulting in a sensitivity of 58% and a specificity of 99.9%. There were five false-positive diagnoses (false-positive rate, 0.06%), all fetal hydronephrosis that presumably resolved after birth.

Sollie and co-workers also reviewed the validity of selection criteria for detecting fetal anomalies with routine sonography.[27] A sensitivity of 60% (73% when minor anomalies were excluded) and a specificity of 93% were demonstrated, compared with a sensitivity of 86% and a specificity of 100% seen in selected patients meeting standard criteria for targeted scans.

Shirley and associates prospectively and retrospectively reviewed 6,183 low-risk women who underwent routine ultrasound studies during pregnancy.[28] Of these women, 87 were found to have fetuses with abnormalities at birth or at induced abortion, and of the 87, 58 had abnormal ultrasound results (sensitivity 67%). There was 1 false-positive diagnosis (specificity 99.9%).

TABLE 3.—*Fetal Malformations That Have Been Diagnosed Prenatally by Ultrasonography*

Cranial and Intracranial
- Agenesis of the corpus callosum
- Anencephaly
- Aqueductal stenosis
- Arachnoid cyst
- Cephalocele
- Choroid plexus cysts
- Communicating hydrocephalus
- Dandy-Walker malformation
- Exencephaly
- Holoprosencephaly
- Iniencephaly
- Intracranial calcification
- Intracranial hemorrhage
- Intracranial neoplasm
- Microcephaly
- Porencephalic cyst
- Schizencephaly
- Unilateral hydrocephalus
- Vein of Galen aneurysm

Craniofacial
- Anophthalmia
- Cyclopia, ethmocephaly, cebocephaly
- Cystic hygroma
- Facial cleft
- Goiter
- Hypertelorism
- Hypotelorism
- Lacrimal duct cyst
- Micrognathia
- Microphthalmia
- Persistent choroidal artery
- Small ears
- Teratoma

Spine
- Hemivertebrae
- Lipomeningocele
- Sacral agenesis
- Sacrococcygeal teratoma
- Scoliosis
- Sirenomelus
- Spina bifida

Thoracic
- Absent lungs
- Bronchial atresia
- Bronchogenic cyst
- Cystic adenomatoid malformation
- Diaphragmatic hernia
- Hydrothorax
- Pulmonary hypoplasia
- Pulmonary sequestration

Gastrointestinal Tract
- Anorectal atresia
- Choledochal cyst
- Cholelithiasis
- Congenital chloridorrhea
- Duodenal atresia
- Enteric duplication cyst
- Hepatic cyst
- Hepatic neoplasm
- Hirschsprung's disease
- Jejunoileal atresia
- Meconium ileus
- Meconium peritonitis
- Mesenteric cyst
- Persistent cloaca
- Situs inversus
- Tracheoesophageal fistula
- Volvulus

Genitourinary System
- Ambiguous genitalia
- Bladder outlet obstruction
- Duplicated kidneys with ectopic ureterocele
- Hydrometrocolpos
- Megacystis microcolon intestinal hypoperistalsis syndrome
- Multicystic dysplastic kidney
- Ovarian cyst
- Pelvic kidney
- Renal agenesis
- Tumors—mesoblastic nephroma, neuroblastoma
- Ureteropelvic junction obstruction
- Ureterovesical obstruction

Cardiovascular System
- Arrhythmias
- Atrioventricular septal defect—endocardial cushion defect
- Cardiomyopathy
- Cardiosplenic syndromes
- Coarctation of the aorta
- Double-outlet right ventricle
- Ebstein's anomaly
- Hypoplastic left ventricle
- Hypoplastic right ventricle
- Pericardial tumors (teratoma)
- Rhabdomyoma
- Tetralogy of Fallot
- Total anomalous pulmonary venous return
- Transposition of the great vessels
- Valvular stenosis
- Ventricular septal defect

Abdominal Wall and Trunk
- Bladder exstrophy
- Cloacal exstrophy
- Ectopia cordis
- Gastroschisis
- Limb-body wall complex (body-stalk anomaly)
- Lymphangioma
- Omphalocele
- Tumors—teratoma, melanoma
- Urachal cyst
- Vascular malformation

Extremities
- Arthrogryposis
- Bone dysplasias
- Clinodactyly
- Clubfeet
- Limb shortening
- Polydactyly
- Radial aplasia

Luck prospectively studied 8,532 low-risk pregnancies with first- and second-trimester ultrasound studies.[29] Of 166 anomalies, 140 were detected (sensitivity 85%). There were 2 false-positive results with a specificity of 99.9%.

Chitty and colleagues retrospectively reviewed 8,432 second- and third-trimester ultrasound studies from low-risk pregnancies.[30] Of these, 125 fetuses were found to have an abnormality at birth or after termination. The authors detected 93 of 125 (sensitivity 74%), with only 2 false-positive diagnoses (specificity 99.9%). The positive predictive value was 97.9%, and the negative predictive value was 99.6%.

These eight studies of ultrasound use in low-risk pregnancies reported sensitivities ranging from 14% to 85% and specificities of 93% or above. This suggests that in low-risk populations, ultrasonography may be helpful in ruling out anomalies, but is not particularly reliable in detecting them.[31] This information may prove useful in counseling patients regarding the accuracy of sonography in the general population.

Studies in High-Risk Populations

Targeted studies appear to be much more accurate. Campbell and Pearce studied 2,372 fetuses at high risk for anomalies because of a positive family history of an abnormality, an abnormal maternal serum α-fetoprotein level, or a suspicious sonogram done elsewhere.[32] They confirmed 405 of 425 anomalies identified prenatally by sonography on postnatal examination, with an overall sensitivity of 95%. Anomalies missed included 9 of 271 central nervous system (CNS) lesions, 2 of 8 cardiac lesions, 5 of 48 gastrointestinal lesions, 3 of 54 genitourinary lesions, and 1 of 21 limb deformities. Furthermore, only 8 false-positive diagnoses were made, involving 4 CNS defects, 3 cardiac defects, and 1 gastrointestinal defect, with an overall specificity of greater than 99%.

Hill and co-workers, scanning both low- and high-risk patients, diagnosed 83 anomalies in 64 neonates.[33] Confirmed at birth were 10 of 10 suspected CNS lesions, 2 of 15 gastrointestinal lesions, 1 of 18 cardiac or chest lesions (although examination of the fetal heart was not routinely done during the years of review), 1 of 13 genitourinary lesions, and 4 of 10 skeletal lesions. There were no false-positive diagnoses. A sensitivity of 27% was reported; because of the nature of the study, specificity could not be calculated.

Manchester and colleagues studied a group of women referred for suspected anomalies and found an overall sensitivity and specificity of 99% and 91%, respectively.[34] Of 257 fetuses, 4 were diagnosed with anomalies not confirmed on neonatal examination (a 1.5% false-positive rate). Of these infants, 2 had been diagnosed with hydronephrosis and 1 with an intracranial cyst, both of which can be dependent on gestational age; the other was diagnosed with an intra-abdominal calcification; 1 of 46 had a lesion (leg amputation) that was not suspected prenatally (2% false-negative rate). Of the newborns with anomalies, 37% had additional malformations either missed or not able to be detected by sonography.

Sabbagha and associates scanned fetuses at high risk for birth defects and demonstrated an overall sensitivity of 95% (78 of 82) and an overall specificity of 99% (509 of 572), with only 4 false-positive results (0.6%) and 3 false-negative results (0.5%)[35] Analyzing the data by organ system, the investigators reported a sensitivity of 94% (30 of 32) and specificity of 99% (140 of 141) with CNS lesions. This agrees with the data of Filly and colleagues who identified 96% (131 of 137) of CNS abnormalities on prenatal sonography.[36] With gastrointestinal lesions, the sensitivity and specificity were 94% (16 of 17) and 100% (22 of 22), respectively. Genitourinary lesions had a sensitivity of 92% (12 of 13) and a specificity of 97% (33 of 34), and skeletal defects a sensitivity of 100% (15 of 15) and a specificity of 100% (6 of 6).

Table 4 compares the detection of malformations in general versus selected populations.[23-30,32-35] The accuracy of ultrasonography varies in the general population, depending on population characteristics. Factors influencing sonography's sensitivity and specificity include the prevalence of an anomaly and the period of postnatal follow-up, as subtle defects may not be apparent immediately after birth.

Accuracy in Diagnosing Congenital Heart Disease

Congenital heart disease is the most common congenital malformation, responsible for most deaths due to congenital anomalies.[37] Yet cardiac defects are especially difficult to identify prenatally and the accuracy of screening examinations even more difficult to assess. The four-chamber view of the heart has been recommended as a screening tool, to be incorporated into routine scans after 16 weeks' gestation in the hope of excluding most cases of congenital heart disease. The sensitivity and specificity of the four-chamber view depends on the population screened and the experience of the sonographer. Fetal echocardiography, a more complex, detailed ultrasound examination of the fetal heart, is recommended only for

TABLE 4.—*Accuracy of Ultrasonography in Detecting Congenital Malformations*

Study	Accuracy	
	Sensitivity, %	Specificity, %
General Population		
Lys et al, 1989[23]	14	98
Li et al, 1988[24]	38	98
Levi et al, 1989[25]	34-55	>99
Rosendahl and Kivinen, 1989[26]	58	>99
Sollie et al, 1988[27]	60-73	93
Shirley et al, 1992[28]	67	>99
Luck, 1992[29]	85	>99
Chitty et al, 1992[30]	74	>99
Selected Population		
Sollie et al, 1988[27]	86	100
Campbell et al, 1983[32]	95	>99
Hill et al, 1985[33]	27	--
Manchester et al, 1988[34]	99	91
Sabbagha et al, 1985[35]	95	99

patients at high risk for carrying fetuses with heart disease. Most fetuses with abnormal echocardiograms are referred because of a suspicious four-chamber view on routine scan,[38] however, and have no other risk factors for congenital heart disease.[39] Risk factors include women with a family history of congenital heart disease, women with diabetes mellitus, a fetus with a suspected abnormality such as a structural defect or an arrhythmia, or women with exposure to teratogenic medications. Referrals for an abnormal four-chamber heart have yielded the greatest number of cases of prenatally detected congenital heart disease at fetal echocardiography centers.

Vergani and co-workers screened 5,336 women, most at low risk for carrying a fetus with congenital heart disease, and were able to obtain a four-chamber view in 95%.[40] Of 32 fetuses with congenital heart disease, 28 had abnormal four-chamber views; 26 of 28 were confirmed by echocardiography, with a sensitivity of 81% and a specificity of 99.9%.

Achiron and colleagues screened 5,347 low-risk fetuses with the four-chamber view and were able to identify 11 of 23 with congenital heart disease (sensitivity 48%).[41] By adding outflow tracts to the four-chamber view, they were able to identify another 7 (sensitivity of 78%). Of 23 fetuses with cardiac defects, 5 were missed, for a false-negative rate of 22%. There was only one false-positive diagnosis, with an overall specificity of greater than 99%. Positive and negative predictive values were 92% to 95% and greater than 99%, respectively.

Sharland and Allan scanned more than 30,000 low-risk pregnancies with the four-chamber view and were able to detect 53 of 69 fetuses with congenital heart disease (sensitivity 77%).[42] There were 96 false-positive results (specificity greater than 99%). Brocks and Bang obtained scans on 9,162 women and diagnosed 6 of 10 fetuses with congenital heart disease (sensitivity 60%).[43] There were no false-positive diagnoses (specificity 100%).

Of these studies, four specifically looked at the accuracy of the four-chamber view in low-risk populations. Reported sensitivities were 36%,[26] 41%,[29] 56%,[28] and 64%.[30] Specificities approaching 100% were noted by all investigators.

Results in Fetal Echocardiography Centers

Allan and colleagues did fetal echocardiographic studies on 89 women whose fetuses were at risk for congenital heart disease.[37] Of those referred, 40 (45%) had suspicious four-chamber views on routine scans done before referral. Of these, more than 80% were confirmed by fetal echocardiogram. No "major" false-positive diagnoses were reported.

Copel and co-workers reported results on 991 women at high risk for carrying fetuses with congenital heart disease[39]: 74 fetuses had heart disease, of which 69 (93%) had abnormal four-chamber views and 71 (96%) had abnormalities potentially detectable by this view. There were 4 false-positive diagnoses, only 1 of which had an abnormal four-chamber view, and 5 false-negative diagnoses, only 1 of which had an abnormal four-chamber view. The sensitivity and specificity in this study were 92% and 99.7%, respectively. Positive and negative predictive values were 96% and 99.4%, respectively. Copel and associates' data reflect a high-risk group of patients scanned by skilled operators experienced in cardiac sonography. Detection rates in low-risk populations scanned by less experienced sonographers are undoubtedly lower than Copel and colleagues' data suggest. Perhaps a four-chamber view of the heart has the potential to diagnose 50% to 60% of major congenital heart disease in a low-risk population.[21] At present, however, only 10% of cases of congenital heart disease are actually detected prenatally.[44] Thus, fetal echocardiography is still recommended for patients at high risk for congenital heart disease. Table 5 reviews the use of the four-chamber view as a screening tool.[26,28-30,40-43]

α-Fetoprotein and Ultrasonography

Maternal serum α-fetoprotein (AFP) levels can be abnormal in a variety of obstetric situations. They may be elevated in women whose fetuses have congenital abnormalities, namely neural tube defects and ventral wall defects, oligohydramnios, abruptio placentae, low birth weight, and fetal or perinatal death. Decreased values may be seen in aneuploid fetuses or in cases of fetal death.[45]

TABLE 5.—*The Four-Chamber View as a Screening Tool in Detecting Congenital Heart Disease*

Study	Accuracy	
	Sensitivity, %	Specificity, %
*General Population**		
Rosendahl and Kivinen, 1989[26]	36	100
Shirley et al, 1992[28]	56	100
Luck, 1992[29]	41	99.9
Chitty et al, 1992[30]	64	100
Vergani et al, 1991[40]	81	99.9
Achiron et al, 1992[41]	48	99.9
Sharland and Allan, 1992[42]	77	>99
Brocks and Bang, 1991[43]	60	100

*Mostly low-risk women were screened.

Elevated Maternal Serum α-Fetoprotein Levels

Most neural tube defects occur in fetuses without risk factors. Maternal serum AFP screening was introduced to identify women at risk for having an infant with a neural tube defect and warranting ultrasonography or amniocentesis. Universal screening has proved to be efficacious[46,47] and is now the standard of care in the United States.

Traditionally, once an elevated maternal serum AFP level is documented, a sonogram is done to ensure that a woman has a viable, singleton pregnancy at the appropriate gestational age. If sonography does not provide an explanation for the elevated AFP level, an amniocentesis is

recommended to assess amniotic fluid AFP and acetylcholinesterase (AChE) to exclude anomalies that sonography may have missed.[48] Recently, with improved detection of congenital anomalies by sonography, this protocol has been reviewed.

Lindfors and associates studied 681 women with elevated maternal serum AFP levels referred to their prenatal diagnostic center for an ultrasound examination.[49] Amniocentesis was offered if the sonogram result was normal or equivocal or if an anomaly associated with a chromosomal abnormality was found. Of 681 women, 442 (68%) underwent amniocentesis; amniocentesis failed in 7, and 71 refused the procedure. Of the 442 patients undergoing amniocentesis, 3 major aneuploidies (47,XYY; mosaic XO; 46,X + centromeric fragment), 2 minor aneuploidies (familial inversion, 46,X with inverted Y), and 3 neural tube defects were found in the group with normal sonograms. Thus the authors recommended offering amniocentesis to patients with elevated maternal serum AFP levels and normal sonograms.

Drugan and colleagues retrospectively studied 321 women with elevated levels of serum AFP referred for an ultrasound examination.[50] Of 321, 64 (20%) were found to have incorrect dates or multiple gestations to account for the AFP elevation. The remaining 257 underwent an amniocentesis. Of these, 20 (8%) had an elevated amniotic fluid AFP level, and 16 of the 20 had anomalies. Of the 16 with anomalies, 15 were positive for AChE, and the other patient had an inconclusive AChE test (defined by the authors as a faint but definite band in the specific position for AChE on gel electrophoresis). Of the remaining 4 patients without anomalies, 3 had inconclusive AChE tests, and 1 had a negative AChE. Of the 16 with anomalies, 12 (75%) were diagnosed by initial ultrasonography (9 of 12 with neural tube defects, and 3 of 4 with other malformations). Early gestational age at the time of initial scanning, smaller defects, and technical failure were reasons given by the authors for the misdiagnoses. They concluded that amniocentesis should remain an essential part of the workup of elevated maternal serum AFP levels, as it identified the remaining 25% of fetal malformations missed initially by sonography.

Schell and associates reviewed 331 patients with "true" elevated levels of maternal serum AFP referred for sonography and amniocentesis.[51] Of these, 36 fetuses with anomalies were identified, 30 of which (83%) were noted on initial ultrasound examination. Repeat sonography done with knowledge of the amniotic fluid AFP and AChE results identified 5 others. The authors concluded that in a patient with an abnormal maternal serum AFP level, a normal sonogram will decrease but not eliminate the possibility of an abnormal fetus. The risk of anomalies and adverse outcomes increases with the degree of AFP elevation, and the odds of having an anomalous fetus with different AFP values and a normal sonogram were calculated for this referral center. The authors recommend amniocentesis only if the maternal serum AFP level is 3 multiples greater than the median, and counsel women with lesser degrees of AFP elevation and a normal ultrasonogram that the risk of amniocentesis may outweigh its benefits.

Richards and colleagues also counsel patients of revised estimates of the risk of neural tube defects based on maternal serum AFP values and a normal sonogram.[52] Assuming a 90% detection rate of neural tube defects based on that institution's data, the risk derived from the maternal serum AFP result is decreased by 90% when the ultrasonogram is reassuring. Amniocentesis is offered to all patients, but only after discussion of the revised risk estimate.

Nadel and co-workers retrospectively reviewed 51 cases of neural tube defects and ventral wall defects where the fetus was either delivered or aborted after an ultrasound study.[53] All 51 had been prenatally diagnosed by sonography (sensitivity 100%), with no false-negative diagnoses. The probability of a neural tube defect or ventral wall defect was then calculated for varying maternal serum AFP levels, both before and after a normal level 2 ultrasound study. The risk of either anomaly was much lower after a normal sonogram. Although other anomalies not addressed in this study are associated with elevated levels of maternal serum AFP, such as Finnish nephrosis, sacrococcygeal teratoma, and fetal skin lesions, these anomalies are rare and need not play a role in the argument for routine amniocentesis and elevated maternal serum AFP levels.

Many screening programs recommend amniocentesis for any pregnancy in which an ultrasound study does not explain an elevated level of maternal serum AFP. At our institution, amniocentesis is offered to all women with an elevated level, but only after a revised risk estimate based on an ultrasound examination is discussed. In our experience, most women decline amniocentesis when the ultrasonogram is normal. With better equipment and increasing skill, potential sensitivity in the diagnosis of anomalies will continue to improve, and current recommendations for an amniocentesis with a mild maternal serum AFP elevation and normal ultrasound may soon prove obsolete.

Decreased Maternal Serum α-Fetoprotein

The association of decreased maternal serum AFP levels and Down syndrome has been well established. A risk determination based on a combination of the maternal serum AFP value and maternal age allows the detection of approximately 30% of fetuses with Down syndrome. With a Down syndrome risk of greater than or equal to 1 in 270 as a cutoff, the use of maternal age in combination with maternal serum AFP, human chorionic gonadotropin, and estriol values may identify 60% of fetuses with Down syndrome. These biochemical markers plus a dating sonogram allow the detection of 67% of Down syndrome fetuses, with a false-positive rate of only 3.8%.

Accuracy in Diagnosing Chromosomal Abnormalities

Chromosome abnormalities are seen in 0.65% of newborns[54] and account for 2.5% to 10% of major congenital

malformations in neonates.[55] It is standard practice to offer prenatal testing to all women 35 years of age or older. Most aneuploidies, however, occur in women younger than 35 without risk factors, who are not candidates for cytogenetic testing. Although routine screening is controversial, it is estimated that two of three pregnant women have at least one sonogram during pregnancy. Therefore, it might be beneficial to be able to detect malformations on ultrasonograms that might suggest chromosomal abnormalities in fetuses of women who are at low risk. Table 6 describes several patterns of malformations seen on sonography that have been associated with chromosomal abnormalities.[56]

Williamson and co-workers, studying 41 high-risk fetuses referred with a broad range of abnormalities on sonogram, found chromosomal anomalies in 13 (32%).[57] Gosden and associates obtained karyotypes in 96 pregnant women referred with sonogram abnormalities, and 27 (28%) were chromosomally abnormal.[58] Platt and colleagues evaluated 63 patients referred because of major malformations seen on sonography.[59] All were offered cytogenetic testing; 20 accepted, and 7 of 20 (35%) were found to have chromosome abnormalities.

TABLE 6.—*Malformations Associated With Chromosomal Abnormalities**

Chromosome Abnormality	*Manifestotion*
Trisomy 21	Duodenal atresia, tracheoesophageal fistula, esophageal atresia; polyhydramnios if these gastrointestinal lesions are present
	Cardiac abnormalities: atrioventricular canal defects, ventricular septal defects, atrial septal defects
	Hypoplasia of the middle quadrant of the 5th digit
	Second-trimester findings: thickened nuchal fold (>6 mm), ratio of actual to expected femur length = 0.91
Trisomy 18	Intrauterine growth retardation
	Polyhydramnios
	Clenched hands with overlapping digits
	Clubfeet, rocker-bottom feet
	Cardiac abnormality: ventricular septal defect
	Omphalocele, diaphragmatic hernia
	Choroid plexus cysts
Trisomy 13	Holoprosencephaly
	Cleft lip and palate
	Cardiac abnormality: ventricular septal defect
	Polydactyly
	Omphalocele
	Polycystic kidneys

*From D'Alton and DeCherney.[56]

These studies reveal an approximately 30% risk of aneuploidy with structural defects. Studies are needed, however, to determine the relative risk of a chromosomal abnormality when a specific malformation is seen on sonography.

Nicolaides and colleagues karyotyped 2,086 high-risk fetuses, most of which had abnormal sonograms, and found 301 (14%) with chromosomal anomalies.[60] The frequency of aneuploidy increased with the number of defects per fetus, approaching 92% when eight or more abnormalities were found.

Benacerraf determined the rate of identification of fetuses with chromosomal abnormalities by reviewing all cases of aneuploidy scanned prenatally.[61] With trisomy 13, 9 of 9 were detected, mainly by craniofacial abnormalities, as were 12 of 15 cases (80%) of trisomy 18, mainly by hand or foot abnormalities. The detection rate of fetuses with Turner syndrome or triploidy was not able to be determined. Certain signs seen on prenatal sonography can be suggestive, however. For instance, cystic hygroma and left-sided heart defects are often seen in fetuses with Turner syndrome, and placental hydrops and intrauterine growth retardation with head-to-body disproportion are often seen in fetuses with triploidy.

Down syndrome is more difficult to detect prenatally. Structural defects such as cardiac and gastrointestinal anomalies are commonly seen in Down syndrome neonates, but can be difficult to diagnose in second-trimester fetuses. For example, 30% of fetuses with duodenal atresia have Down syndrome, but only 3% to 8% of fetuses with Down syndrome have detectable upper gastrointestinal tract obstructions. Moreover, although the ultrasonographic diagnosis of duodenal atresia is readily made after 28 weeks' gestation, its consistent diagnosis may be difficult or impossible before 24 weeks' gestation. Thus, duodenal atresia, which is suggestive of Down syndrome, is not a useful ultrasonographic marker in most cases. Further, cardiac defects are found in 50% of fetuses with Down syndrome, but as previously discussed, these can be difficult to detect during routine screening.

Nuchal thickening, shortened femur length, and dysplasia of the midphalangeal ossification center of the fifth finger have been touted by some as sensitive indicators of Down syndrome. Ultrasound detection is hindered by the subtlety of these findings, however, requiring substantial technical skill. Furthermore, there is considerable overlap of these features with the unaffected population. Table 7 compares present screening techniques.[62-70]

Thickened Nuchal Fold

Nuchal thickening in a second-trimester fetus is usually defined as 6 mm or more from the outer aspect of the occipital bone to the outer aspect of the skin edge. Most studies evaluating nuchal thickening have been retrospective in nature, reviewing sonograms of fetuses known to have Down syndrome by amniocenteses. Benacerraf and co-workers first described a correlation between nuchal thickening seen on prenatal ultrasound and Down syndrome.[71] Of 3,825 fetuses whose mothers underwent amniocenteses for various indications, 21 were found to have trisomy 21. Of 21, 9 (43%) had nuchal thickening on sonography. Of 3,825 fetuses without trisomy 21, 4 also had nuchal thickening; 1 had an abnormal karyotype other than Down syndrome, and 3 had normal karyotypes, resulting in a false-positive rate of 0.1%. In a

TABLE 7.—*Detection of Down Syndrome: Screening Techniques*

Screening Factor	Accuracy: Detection Rate, %	Accuracy: False-Positive Rate, %
Advanced maternal age, ≥35 years	20-25	5
Maternal serum α-fetoprotein (AFP)	25	5
Maternal serum AFP, human chorionic gonadotropin (hCG), and unconjugated estriol (triple screen)	58	6.6
Dating ultrasonogram plus maternal serum AFP, hCG, and unconjugated estriol	67	3.8
Nuchal thickening		
Benacerraf et al, 1991[62]	43	0-0.1
Nyberg et al, 1990[63]	16	0.3
Perella et al, 1988[64]	21	9-11
Shortened femur		
Benacerraf et al, 1987[65]	68	2
Nyberg et al, 1990[66]	14	6
Lockwood et al, 1987[67]	51-70	5-7
Perella et al, 1988[64]	26	23
Brumfield et al, 1989[68]	40	2
Dickie et al, 1989[69]	15-18	4-10
Hill et al, 1989[70]	36	15

continuation of the above study, 28 fetuses with Down syndrome were detected in 5,500 undergoing amniocentesis.[65] Of the 28 affected, 12 (43%) had nuchal thickening. None of 192 controls had nuchal thickening.

Benacerraf and colleagues have also prospectively studied 36 second-trimester fetuses found to have nuchal thickening with no other risk factors for aneuploidy. Of 36 fetuses, 8 (22%) had abnormal karyotypes: 5 with Down syndrome, 1 with Turner syndrome, 1 with XYY and 1 with XXX. None of these patients would otherwise have been candidates for cytogenetic testing.[62] Based on these data, the finding of nuchal thickening on second-trimester sonography should prompt an amniocentesis for definitive diagnosis. The effect of gestational age on the extent of nuchal thickening has not been evaluated as thoroughly, although preliminary data suggest that first-trimester nuchal thickening may also play a role in the detection of aneuploid fetuses.

Other centers have done similar studies but have been unable to duplicate such high sensitivities and specificities. Nyberg and co-workers reported nuchal thickening in 4 (16%) of 25 fetuses with Down syndrome and only 1 (0.3%) of 350 normal controls.[63] The positive predictive value in the general population based on this study was 8%. Perella and associates reviewed the sonograms of 28 fetuses with Down syndrome and compared them with 128 controls.[64] Of the 28, 15 had satisfactory views of the posterior fossa to enable assessment of nuchal thickening; one of these was excluded because of a cystic hygroma. Of 14 fetuses with Down syndrome, 3 (21%) had thickened nuchal folds, as did 12 (9%) of 108 chromosomally normal fetuses.

Fetal Biometry and Down Syndrome

In a continuation of a previous study, Benacerraf[65] performed regression analysis to evaluate the relationship between biparietal diameter and femur length and found 19 of 28 (68%) fetuses to have an actual-to-expected femur length ratio of 0.91 or less, with a specificity of 98%. When the data on nuchal thickening were combined with those of actual-to-expected femur lengths, the sensitivity increased to 75% and the specificity remained 98%. Of note, 17 of 28 (61%) had thickened nuchal folds, shortened femurs, or both, as the only sonographic abnormality.

The positive predictive value of an abnormal sonographic finding differs according to the prevalence of Down syndrome in the population. In the above study, where the risk of Down syndrome in the general population was thought to be 1 in 500, the positive predictive value was 7%; in a high-risk population, for instance, in women of age 35, the risk of Down syndrome is 1 in 250 and the positive predictive value is 13%. These numbers fare favorably when compared with predictive values based on advanced maternal age or low maternal serum AFP levels, and thus amniocentesis is recommended by these authors when either a thickened nuchal fold or shortened femur is seen on second-trimester sonography.

Nyberg and co-workers compared 49 fetuses with Down syndrome with 572 chromosomally normal fetuses.[66] Using an equation comparing biparietal diameter and femur length similar to that of Benacerraf and associates, 7 of 49 (14%) fetuses with Down syndrome were found to have a short femur length (actual-to-expected ratio of ≤ 0.91) compared with 35 of 572 (6%) controls. This difference was statistically significant. The positive predictive value was only 0.3% in a low-risk population (prevalence of Down syndrome 1 in 700) and 0.9% in a high-risk population (women aged 35, with a prevalence of Down syndrome of 1 in 250). Although this study supports a relationship between short femur length and Down syndrome, it does not appear to justify doing amniocentesis in women who are otherwise at low risk.

Lockwood and colleagues compared 55 fetuses with Down syndrome with 544 controls and found that a biparietal diameter-to-femur length ratio of at least 1.5 standard deviations (SD) identified between 51% and 70% of Down syndrome fetuses, with a false-positive rate of only 5% to 7%.[67] The positive predictive value varied from 1% to 2% in a low-risk population to 3% to 6% in a high-risk population. These results compare favorably with both advanced maternal age and maternal serum AFP screening programs. Furthermore, they identify a larger proportion of fetuses with Down syndrome with fewer amniocenteses and thus encourage each center to establish its own second trimester biparietal diameter-to-femur length curves in chromosomally normal fetuses to aid in assessing the risk of Down syndrome.

In a previously mentioned study, Perella and associates reviewed the ultrasound studies of 19 fetuses with Down syndrome having satisfactory biparietal diameter and femur length measurements.[64] Of 19 fetuses, 5 (26%)

had actual-to-expected femur length ratios of 0.91 or less, as did 28 of 128 (23%) controls. The overall sensitivity and specificity in this study were 42% and 88%, respectively. The positive predictive value in a high-risk population was only 1.4%.

Brumfield and co-workers reviewed the sonograms of fetuses with Down syndrome and compared them with those of 45 normal controls.[68] A 40% sensitivity and a 98% specificity in predicting Down syndrome was found when a biparietal diameter:femur length ratio of 1.80 or more was used. The false-positive rate in this study was 2.2%.

Dickie and associates examined the biparietal diameter:femur length ratio and the actual-to-expected femur length ratio in 48 second-trimester fetuses with Down syndrome and compared them with chromosomally normal fetuses.[69] A ratio of biparietal diameter to femur length of greater than 1.5 SD resulted in a sensitivity of 18%, a false-positive rate of 4%, and a positive predictive value of 0.6%. An actual-to-expected femur length ratio of 0.91 or less resulted in a sensitivity of 15%, a false-positive rate of 10%, and a positive predictive value of 0.2%.

Hill and colleagues reviewed sonograms of 22 fetuses with Down syndrome and found the ratio of biparietal diameter to femur length to be more helpful in identifying fetuses with Down syndrome than either nuchal thickening or the actual-to-expected femur length.[70] Of 22 fetuses, 8 had ratios of greater than 1.5 SD, resulting in a sensitivity of 36% and a specificity of 93%. The positive predictive value in a low-risk population was 0.6%, while in a high-risk population it was 2%. Of 22 fetuses, 11 (50%) had neither nuchal thickening nor shortened femurs by either the biparietal diameter:femur length ratio or actual-to-expected femur length ratio.

The explanation for these differing results is unclear. Biologic differences in long-bone lengths between unaffected fetuses and those with Down syndrome may not be of sufficient magnitude to allow discrimination by second-trimester sonography. Fitzsimmons and colleagues assessed postmortem fetal long-bone lengths, either directly or by radiologic studies, in unaffected and Down syndrome fetuses.[72] Small but significant differences between femur lengths were seen. Actual-to-expected femur length ratios of less than 0.91 detected only 6 of 37 (16%) abortuses with Down syndrome. The false-positive rate was not reported.

Down syndrome is also associated with hypoplasia or dysplasia of the fifth finger. Benacerraf and co-workers observed hypoplasia of the midphalangeal ossification center with concomitant clinodactyly of the fifth finger in three of four (75%) second-trimester fetuses with Down syndrome.[73] In a subsequent study, the same group compared the ratio of fifth digit to fourth digit midphalangeal ossification center lengths in 1,024 unaffected fetuses and in eight fetuses with Down syndrome.[74] The mean ratios were 0.85 and 5.9, respectively. A ratio of 0.7 or less identified six of eight fetuses (75%) with Down syndrome; the false-positive rate was 18%. Given the technical skill and state-of-the-art equipment required to make such small measurements, however, this approach is unlikely to have immediate widespread application.

Second-trimester ultrasonography does not appear to be sensitive or specific enough to be used alone in Down syndrome screening. Sonographic assessment of nuchal fold thickness and fetal biometry, however, may complement maternal age and biochemical markers in the assignment of Down syndrome risk.

Choroid Plexus Cysts

Choroid plexus cysts are seen on ultrasonograms in 0.2% to 2.5% of normal fetuses, depending on the gestational age of the fetus at the time of the scan. An association with aneuploidy was first described in 1986 by Nicolaides and co-workers, who noted that three of four fetuses with choroid plexus cysts had trisomy 18.[75] Since then, many studies have looked at the incidence of chromosomal abnormalities with choroid plexus cysts; these are summarized in Table 8.[60,75-89]

The most important factor in predicting a chromosomally abnormal fetus when a choroid plexus cyst is found is the presence of associated anomalies. Large, complex, multiple or bilateral cysts may increase the likelihood of carrying a chromosomally abnormal child. The actual risk of abnormalities with isolated choroid plexus cysts is unknown. Current recommendations when seen on sonograms include a thorough search for other anomalies. An amniocentesis is indicated if other anomalies are found. With an adequate and otherwise normal ultrasound examination, however, an amniocentesis may not be warranted.

There has been only one published report of an isolated, solitary, unilateral cyst of less than 1 cm associated with a chromosomal anomaly. Because of technical difficulties, it is unclear if the contralateral choroid plexus was adequately examined.[89]

Ultrasonography and Fetal Assessment

Ultrasonography is used extensively to evaluate fetal well-being. Manning and co-workers developed a bio-

TABLE 8.—*Incidence of Aneuploidy and Choroid Plexus Cysts*

Study	*Patients, No.*	*Chromosomal Anomalies*	*Associated Anomalies*
Chuldleigh et al, 1984[76]	5	0	0
Nicolaides et al, 1986[75]; 1992[60]	121	34	33 of 34
Ricketts et al, 1987[77]	4	1	1
Ostlere et al, 1987[78]; 1989[79]; 1990[80]	100	3	3
Chitkara et al, 1988[81]	41	1	1
DeRoo et al, 1988[82]	16	0	0
Benacerraf and Laboda, 1988[83]	38	0	0
Clark et al, 1988[84]	5	0	0
Gabrielli et al, 1988[85]	82	4	4
Chan et al, 1989[86]	13	0	0
Chinn et al, 1990[87]	38	1	1
Platt et al, 1990[88]	71	4	4
Perpignano et al, 1991[89]	83	6	1 of 6

physical profile to assess fetal health after 26 weeks' gestation.[90] This test evaluates five fetal variables: tone, movement, breathing, heart rate pattern (nonstress test), and amniotic fluid volume. These variables are mediated by the central nervous system, which is sensitive to hypoxemia and asphyxia. Loss of any of the first four variables may be indicative of acute asphyxia, whereas the presence of the above factors indicates an intact central nervous system. A decrease in amniotic fluid volume may indicate chronic asphyxia.

Behaviors present the earliest in fetal development are the most resistant to asphyxia. Thus, alterations in fetal heart rate variability and reactivity occur first, followed by the loss of fetal breathing, movement, and then tone. The gestational age of the fetus may be important to consider when evaluating biophysical variables, especially in the preterm fetus, as certain variables tend to be more or less prominent with increasing gestational age.[91]

The incidence of low five-minute Apgar scores is significantly greater with at least one abnormal biophysical profile variable, as compared with normal test results. Fetal acidosis, defined as umbilical cord blood pH of less than 7.20, is also more common,[92] as is fetal distress in labor.[93] Most important, compared with a control group with a corrected perinatal mortality ranging from 8.8 to 40.6 in 1,000, the corrected perinatal mortality in a population screened with biophysical profiles is significantly lower, ranging from 1.9 to 12.6 in 1,000, depending on the study.[94]

TABLE 9.—*Biophysical Profile Scoring**

Biophysical Variable	*Normal (Score = 2)*	*Abnormal (Score = 2)*
Fetal breathing movements	At least 1 episode of >30 seconds' duration in 30 minutes' observation	Absent or no episode of ≥30 seconds' duration in 30 minutes
Gross body movements	At least 3 discrete body or limb movements in 30 minutes (episodes of active continuous movement considered a single movement)	Up to 2 episodes of body or limb movements in 30 minutes
Fetal tone	At least 1 episode of active extension with return to flexion of fetal limb(s) or trunk; opening and closing of hand considered normal tone	Either slow extension with return to partial flexion or movement of limb in full extension or absent fetal movement
Reactive fetal heart rate	At least 2 episodes of acceleration of ≥15 bpm and 15 seconds' duration associated with fetal movement in 30 minutes	Fewer than 2 accelerations or acceleration <15 bpm in 30 minutes
Qualitative amniotic fluid volume	At least 1 pocket of amniotic fluid measuring 2 cm in 2 perpendicular planes	Either no amniotic fluid pockets or a pocket <2 cm in 2 perpendicular planes

*Adapted from Manning et al.[90]

TABLE 10.—*Fetal Outcome in Relation to the Fetal Biophysical Profile Score*†*

		Outcome		*Abnormal*			
Score	*No. (%)*	*Normal, No. (%)*	*Abnormal*	*Perinatal Mortality*	*Fetal Distress*	*5-Min Apgar <7*	*SGA*
10	224 (78)	211 (94)	13	2	4	4	3
8	45 (16)	39 (87)	6	0	5	2	0
6	10 (4)	7 (70)	3	0	3	1	1
4	4 (1)	1 (25)	3	0	1	0	2
2	3 (1)	0 (0)	3	2	1	0	0

SGA = small for gestational age

*Biophysical profile score versus numbers of abnormal outcome diagnosis. Some fetuses had >1 abnormal outcome diagnosis. See text for calculating the score.
†From Platt et al.[93]

TABLE 11.—*Biophysical Variables and Biophysical Profile Score Versus Perinatal Death**

	Test Result		*Perinatal Death*		
Biophysical Variable	*Normal (%)*	*Abnormal (%)*	*Normal (%)*	*Abnormal (%)*	*Likelihood Ratio*
Nonstress test	3644 (87.1)	540 (12.9)	13 (0.4)	19 (3.5)	4.7
Fetal breathing movements	3936 (94.0)	248 (6.0)	23 (0.6)	9 (3.6)	4.9
Fetal movements	4147 (99.1)	37 (0.9)	22 (0.3)	10 (27.0)	48.1
Fetal tone	4067 (97.2)	117 (2.8)	18 (0.4)	14 (12.0)	17.6
Amniotic fluid volume	4138 (98.9)	46 (1.1)	29 (0.7)	3 (6.5)	9.1
Normal biophysical profile score (BPS)	4079 (97.5)		17 (0.4)		0.5
Equivocal BPS	66 (1.6)		4 (6.0)		8.4
Abnormal BPS	39 (0.9)		11 (28.2)		51.0

*From Baskett et al.[97]

Table 9 details the biophysical profile scoring method.[90] The highest score a fetus can receive is 10 of 10, the lowest 0 of 10. Pregnancy management depends not only on the results of the biophysical profile, but also on the gestational age of the fetus and any other complicating factors. Clinical circumstances of each case must play a role in management decisions.[95] The false-positive rate can be high, ranging from 44%[96] to 72%,[97] and probably reflects the normal periodicity of any given variable. As depicted in Tables 10 and 11, as the number of abnormal variables increases, the false-positive rate decreases, with fetal asphyxia or death more likely.[93,97] The false-negative rate, defined as the number of stillbirths within a week of a normal test, is generally low, ranging from 0.4 to 0.7 of 1,000, which is comparable to that of the contraction stress test and lower than that of the nonstress test alone.

Summary

The safety of ultrasonography in pregnancy is well documented. In screening populations, sonography can diagnose approximately 50% of major anomalies, and the accuracy will undoubtedly improve with increasing operator experience and continued improvement in equipment resolution. The ability of sonography to affect perinatal outcome in low-risk pregnancies has not been borne out in available studies, and therefore its role in routine screening remains controversial. In targeted populations, ultrasonography's accuracy in diagnosing congenital anomalies is well over 90%. The prenatal detection of abnormalities often influences obstetrical management and optimizes the care of the fetus and newborn. The ability of sonography to determine gestational age, detect multiple gestations, and assess fetal well-being by diagnosing growth abnormalities, fluid abnormalities, and abnormal biophysical variables has changed the practice of obstetrics more than any other technology in recent years.

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Cardiac Ultrasonography in Structural Abnormalities and Arrhythmias

Recognition and Treatment

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Fetal cardiac ultrasonography has become an important tool in the evaluation of fetuses at risk for cardiac anomalies. It can both guide prenatal treatment and assist the management and timing of delivery. We recommend that a fetal echocardiogram be done when there is a family history of congenital heart disease; maternal disease that may affect the fetus; a history of maternal drug use, either therapeutic or illegal; evidence of other fetal abnormalities; or evidence of fetal hydrops. The optimal timing of evaluation is 18 to 22 weeks' gestation. An entire range of structural cardiac defects can be visualized prenatally, including atrioventricular septal defect, ventricular septal defect, cardiomyopathy, ventricular outlet obstruction, and complex cardiac defects. The outcome for a fetus with a recognized abnormality is unfavorable, with less than 50% surviving the neonatal period. Fetal cardiac arrhythmias are also a common occurrence, 15% in the series described here. Premature atrial or ventricular contractions are most commonly seen and usually require no treatment. Supraventricular tachycardia can result in hydrops and require in utero treatment to prevent fetal demise. Complete heart block, particularly in association with structural heart disease, has a poor prognosis for fetal survival.

(Brook MM, Silverman NH, Villegas M: Cardiac ultrasonography in structural abnormalities and arrhythmias—Recognition and treatment, *In* Fetal Medicine [Special Issue]. West J Med 1993; 159:286-300)

Cardiac ultrasonography in fetuses at risk has assumed a major role in the diagnosis and treatment of prenatal disorders. Structural defects occur in about 8 of 1,000 live newborns[1,2] and more frequently in other situations, making cardiac defects one of the more common fetal abnormalities. The development of high-resolution ultrasound scanners that provide two-dimensional imaging, real-time directed M mode, Doppler, and color Doppler capabilities[3] has enabled structural defects,[4-17] arrhythmias,[18-24] and abnormal cardiac function[25-29] to be recognized in fetuses as early as 16 to 18 weeks. The presence of substantial cardiac defects may determine the site and route of delivery that is best for both fetus and mother. In addition, the availability of high-resolution cardiac ultrasonography adds to the scope of genetic counseling, including the possibility of therapeutic abortion in certain patients, and allows the monitoring of arrhythmias during the administration of antiarrhythmic agents, either transplacentally or directly. As advances in cardiac surgical procedures present the possibility of fetal cardiac operations, prenatal cardiac ultrasonography will be of even greater importance.[30-32]

Methods

Indications for Fetal Cardiac Ultrasonography

We use the following indications for fetal echocardiography[15]:

- *Previous occurrence of congenital heart disease in siblings or parents.* If more than one child has been affected previously, or if the mother or father also has congenital heart disease, then the rate of recurrence increases.[33-35]
- *Maternal diseases known to affect the fetus,* such as diabetes mellitus or connective tissue disease, are important indications for fetal echocardiography. For instance, euglycemic control at the time of conception and in early pregnancy may reduce the risk of cardiac maldevelopment and of fetal diabetic cardiomyopathy, which can be recognized before or after birth.
- *Maternal drug use.* Many drugs give rise to fetal abnormalities, including cardiac abnormalities, when ingested during pregnancy. These include alcohol, lithium carbonate, antitumor drugs, certain anticonvulsants, and warfarin sodium.[36]
- *Abnormalities of other fetal systems,* such as chro-

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mosomal abnormalities, diaphragmatic hernia, omphalocele, polyhydramnios or oligohydramnios, and other systemic anomalies, are indications for fetal echocardiography. When other fetal abnormalities have been detected by obstetric ultrasound examination,[37] especially nonimmune hydrops, omphalocele, or diaphragmatic hernia, structural cardiac defects are more frequently detected. Information derived from fetal echocardiography has a direct bearing on care during the pregnancy. In a cohort of 3,016 pregnancies, Smythe and co-workers found 170 fetuses with heart disease, of which 55 (32%) had extracardiac abnormalities and 45 (28%) had chromosomal disease.[38]

• *Hydrops, nonimmune hydrops.* Many fetuses referred for nonimmune hydrops (16.5% to 22.0%) have cardiac disease as well.[25,39,40] Hydrops has a low incidence of survival, particularly with cardiac disease; Smythe and associates reported fatalities in seven of seven cases of nonimmune hydrops with cardiac disease.[38]

• *Abnormalities of fetal heart rhythm: tachycardia or*

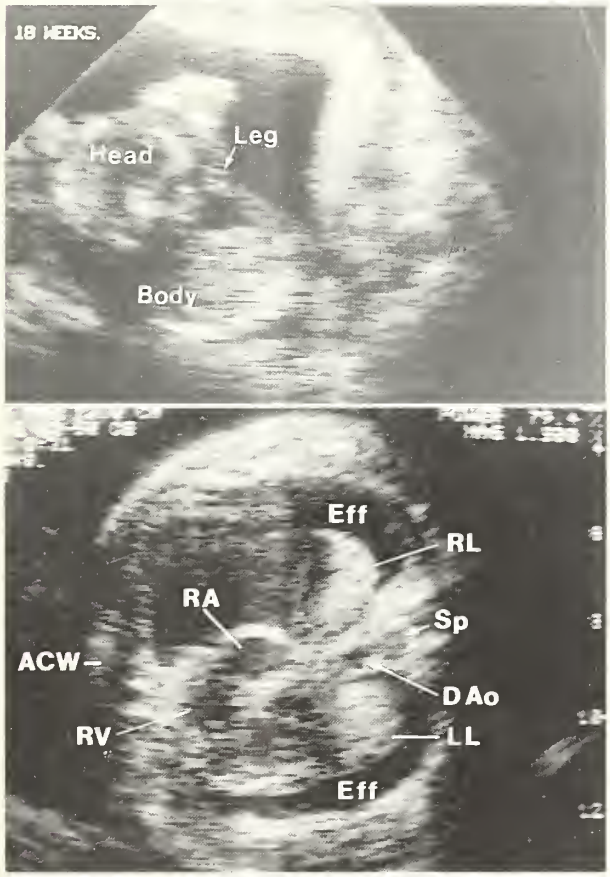

Figure 1.—**Top,** An unmagnified sonographic view is shown of the fetus lying within the uterine cavity at 18 weeks' gestation. The head, legs, and body can be seen clearly, and the orientation of the heart is established in the thorax by referring to its position with regard to the fetal lie. **Bottom,** A magnified transverse ultrasonographic view through the fetal heart (four chambers) and thorax is shown in a fetus with nonimmune hydrops and pleural effusions **(Eff)** surrounding the right lung **(RL)** and left lung **(LL)**. The right ventricle **(RV)** is seen close to the anterior chest wall **(ACW)**, whereas the left atrium lies more posteriorly in front of the descending aorta **(D Ao)** and the spine **(Sp)**. The right atrium **(RA)** lies behind the right ventricle **(RV)**. In this and most subsequent echocardiographic images, a centimeter scale marker is shown to the right of the figure.

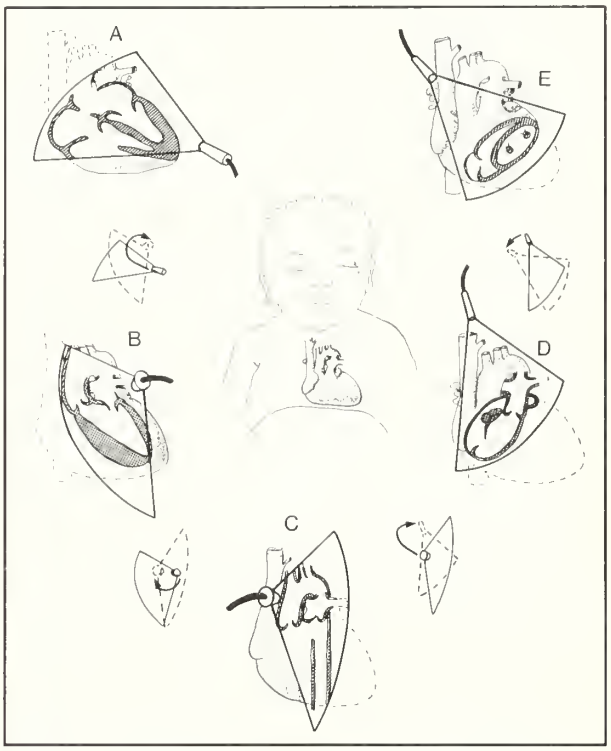

Figure 2.—The drawing schematically represents various views used to image the fetal heart. The heart is oriented more horizontally than after birth (center). Although all views show imaging through the abdomen, this is possible from the back. **A,** A 4-chamber view shows both atria and ventricles and the atrioventricular valves. **B,** The long-axis view shows the left ventricular outflow tract. **C,** Sagittal views show the pulmonary bifurcation, the aortic arch, and the ductal arch. **D,** Short-axis images allow visualization of the right ventricular outflow tract. **E,** Apical short-axis planes show the ventricular structure and the papillary muscles of the left ventricle (from Schmidt and Silverman, reprinted with permission[48]).

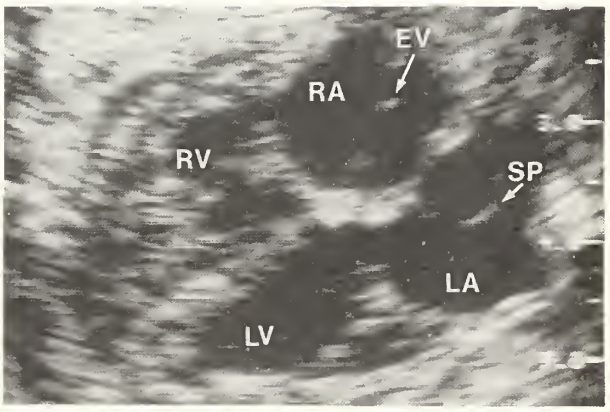

Figure 3.—This fetal 4-chamber view is similar to the plane of Figure 2-A and demonstrates the cardiac chambers and the eustachian valve **(EV)** within the right atrium **(RA)** and the septum primum **(SP)** within the left atrium **(LA)** (from Schmidt and Silverman, reprinted with permission[49]). **LV** = left ventricle, **RV** = right ventricle

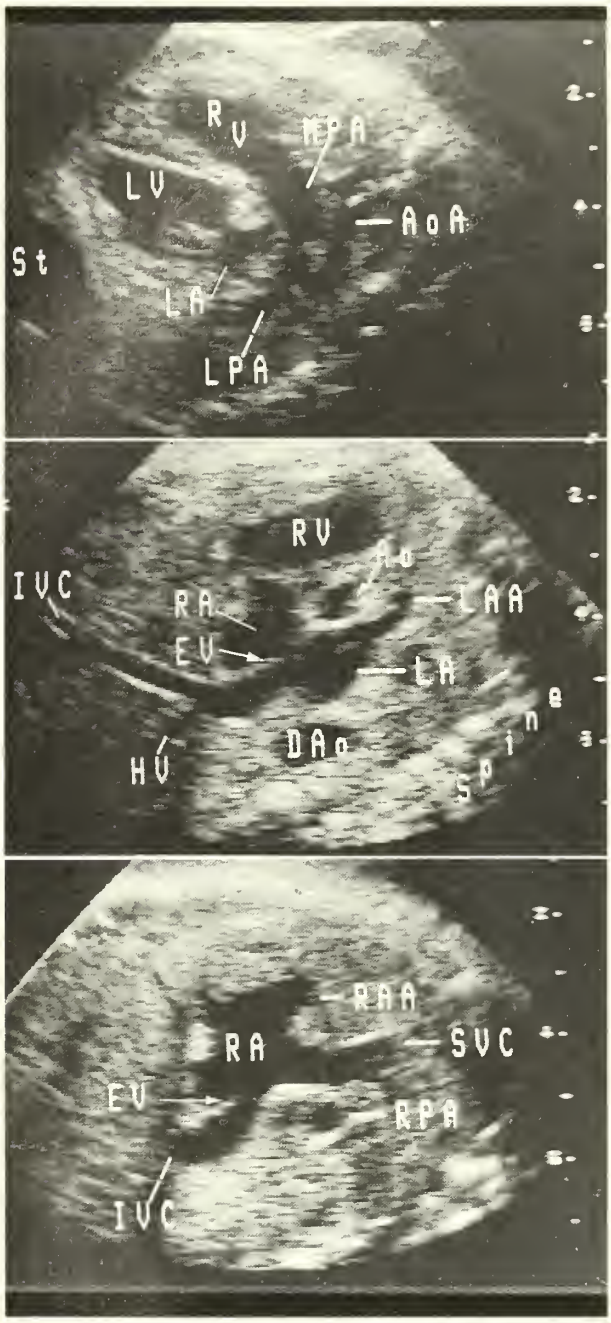

Figure 4.—These images represent a sweep in the sagittal plane from left to right. **Top,** The most leftward cut shows the right ventricle **(RV)** connected to the main pulmonary artery **(MPA)** and the proximal left pulmonary artery **(LPA)**. The left atrium **(LA)**, left ventricle **(LV)**, and a portion of the aortic arch **(AoA)** can be seen, but their connections are not clear. **Middle,** A midline view (note **Spine** to the right) shows the inferior vena cava **(IVC)** and hepatic veins **(HV)** connecting to the right atrium **(RA)**, and the right venous valve or eustachian valve **(EV)**. The left atrium **(LA)**, with its fingerlike appendage **(LAA)**, and the ascending **(Ao)** and descending **(DAo)** aorta and right ventricle **(RV)** are also visualized. **Bottom,** Furthest to the right can be seen both the superior **(SVC)** and inferior **(IVC)** vena cavae draining into the right atrium **(RA)**, with its broad atrial appendage **(RAA)**. A cross-section of the right pulmonary artery **(RPA)** is seen posterior to the SVC (from Schmidt et al, reprinted with permission[50]). **St** = stomach

bradycardia. Congenital heart block is likely in the presence of a slow fetal heart rate (< 80 beats per minute). To evaluate the arrhythmia and to detect structural cardiac defects, if present, fetal echocardiography should be performed. In association with structural cardiac defects, complete heart block has an extremely poor prognosis, presumably because of the adverse interaction of structural defects and bradycardia. The mothers of fetuses with complete heart block, but without structural cardiac defects, frequently are afflicted with a connective tissue disorder, either overt or covert clinically.[24,41,42] This can be substantiated by obtaining maternal serum specimens for anti-Ro and anti-La antibodies or anti-DNA antibodies, which have been found in a variety of collagen vascular diseases that produce congenital heart block. In our experience, other arrhythmias have no higher association with any structural abnormality of the heart.[24] Tachycardias in utero are associated with heart failure, nonimmune hydrops, and fetal loss. The transplacental administration of antiarrhythmic drugs has proved to be of substantive value for the survival of these fetuses.

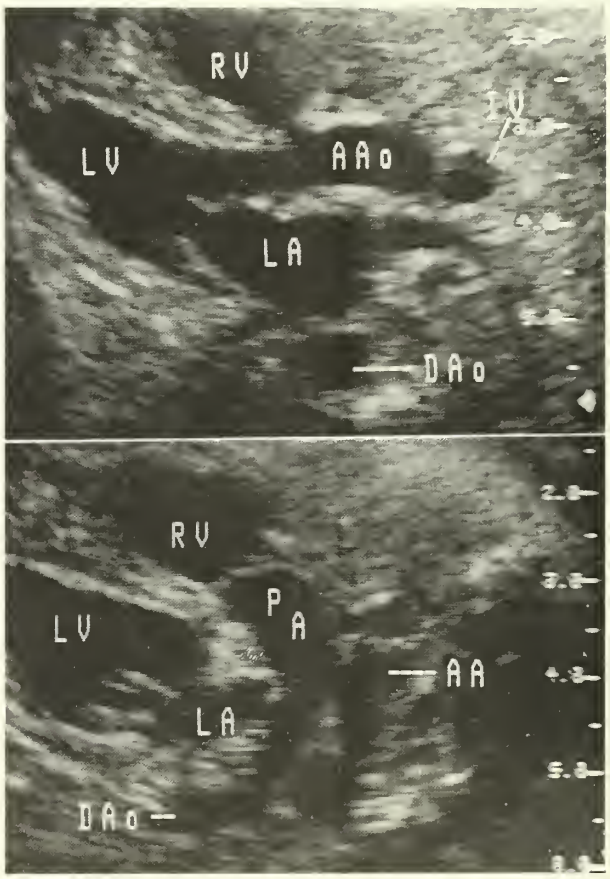

Figure 5.—Long-axis images allow imaging of the ventriculoarterial anatomy (see Figure 6). **Top,** A standard long-axis image shows the entire left system. The left atrium **(LA)** drains to the ventricle **(LV)**, which gives rise to the ascending aorta **(AAo)**. The innominate vein **(IV)** and descending aorta **(DAo)** are seen in cross-section, as is a portion of the right ventricle **(RV)**. **Bottom,** A more leftward image shows the right ventricle **(RV)** connecting to the pulmonary artery **(PA)** inferior to the aortic arch **(AA)** (from Schmidt et al[50]).

When to Perform a Fetal Echocardiogram

We prefer to do an elective evaluation between 18 and 22 weeks' gestation because the valves are well developed, the heart is of adequate size for study, and the fetal size and position usually allow the best access to the heart. Although the incidence of successful imaging is less than at 18 to 22 weeks, successful echocardiographic examination of the heart can be done as early as the 16th week. Intravaginal ultrasound transducers may provide excellent imaging even earlier. If the mother must terminate the pregnancy because of a major abnormality, this information needs to be imparted before the 24th week of the pregnancy.

Equipment

The cornerstone of fetal echocardiography is a high-resolution ultrasound imaging system equipped with M-mode, pulsed Doppler, continuous wave, and color flow Doppler ultrasound. Doppler ultrasonic energy should be kept at or below 100 mW per cm^2 (spatial peak-temporal average), and Doppler interrogation should be limited to as short a time as possible.[43,44]

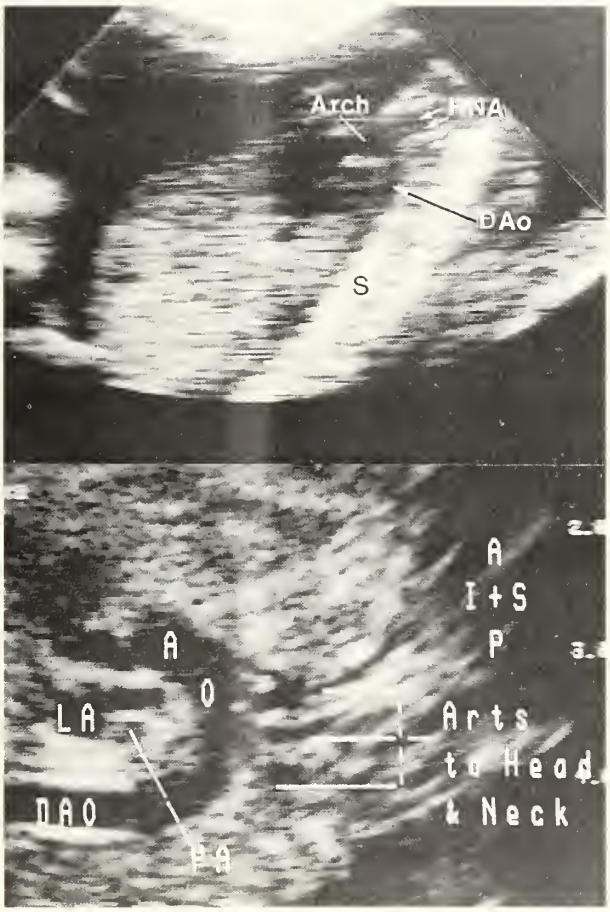

Figure 6.—The top frame shows the entire aortic arch and descending aorta **(DAo)** lying anterior to the spine **(S)**. The vessels to the head and neck **(HNA)** can be seen arising from the superior surface. The bottom frame shows a larger view of the arch. The three arteries to the head and neck are clearly visualized. The left atrium **(LA)** and right pulmonary artery **(PA)** can be seen in the concavity of the arch. Note that the "ductus arch" cannot be seen in this view. **Ao** = ascending aorta

Examination Technique

Cross-sectional Scanning

To define the cardiac position and site, the cross-sectional image must be oriented to the fetal body by noting the position of the head, body, and limbs. An estimated fetal age, using biparietal diameter or femoral length measurements, is also important because cardiac dimensions relate to gestational age and fetal weight.[5,45-47] Imaging the heart through the fetal abdomen usually provides the highest resolution (Figures 1 through 8[48-50]); however, this imaging can be done through the back and rib cage because the fetal lungs are filled with fluid and thus do not generate echo reflections as they do postnatally.

Doppler Color Flow Mapping

Recently the use of color flow mapping has added another dimension to cardiac evaluation,[3] allowing the rapid detection of stenotic or regurgitant jets and thereby diminishing the time required for Doppler interrogation. Different techniques from postnatal echocardiography are used to define the low-velocity signals found in many of the fetal chambers and vessels, as the amount and velocity of flow are substantially less.

Doppler Echocardiography

Pulsed Doppler echocardiography is obtained from the real-time scan with superimposed Doppler color flow imaging. Doppler interrogation within vascular structures

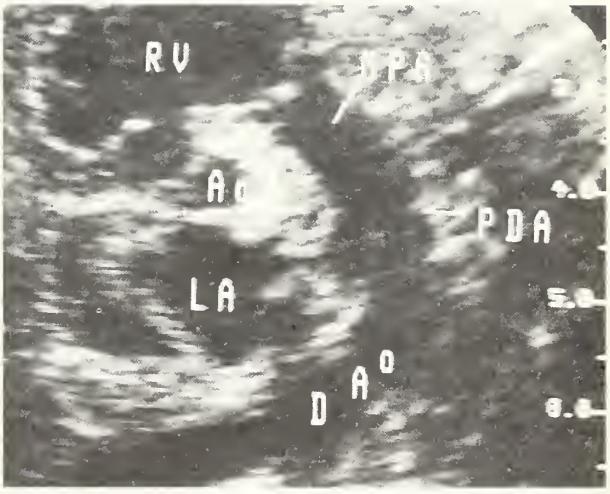

Figure 7.—A magnified fetal sagittal view at 36 weeks' gestation shows the continuation of the main pulmonary artery **(MPA)**, ductus arteriosus **(PDA)**, and descending aorta **(DAo)**, the so-called ductus arch. The ascending aorta **(Ao)** is seen in cross-section; the origin of the left pulmonary artery branch is seen, but the main continuation of the ductus continues as an arch into the descending aorta. Note that the ductus at this stage of gestation appears to be narrower than the caliber of pulmonary artery or the descending aorta. The other structures identified in this view are the right ventricle **(RV)** and a small portion of the left atrium **(LA)**.

identifies arterial or venous flow (Figures 9 and 10) and defines the direction of blood flow in complex cardiovascular malformations. Normal flow velocity profiles have been defined in the fetus across both the atrioventricular and the semilunar valves.[51-57] As after birth, when the velocity of the pulsed-mode Doppler is exceeded, we use continuous-mode Doppler to define the peak velocity for assessing pressure drops across stenotic or regurgitant valves.

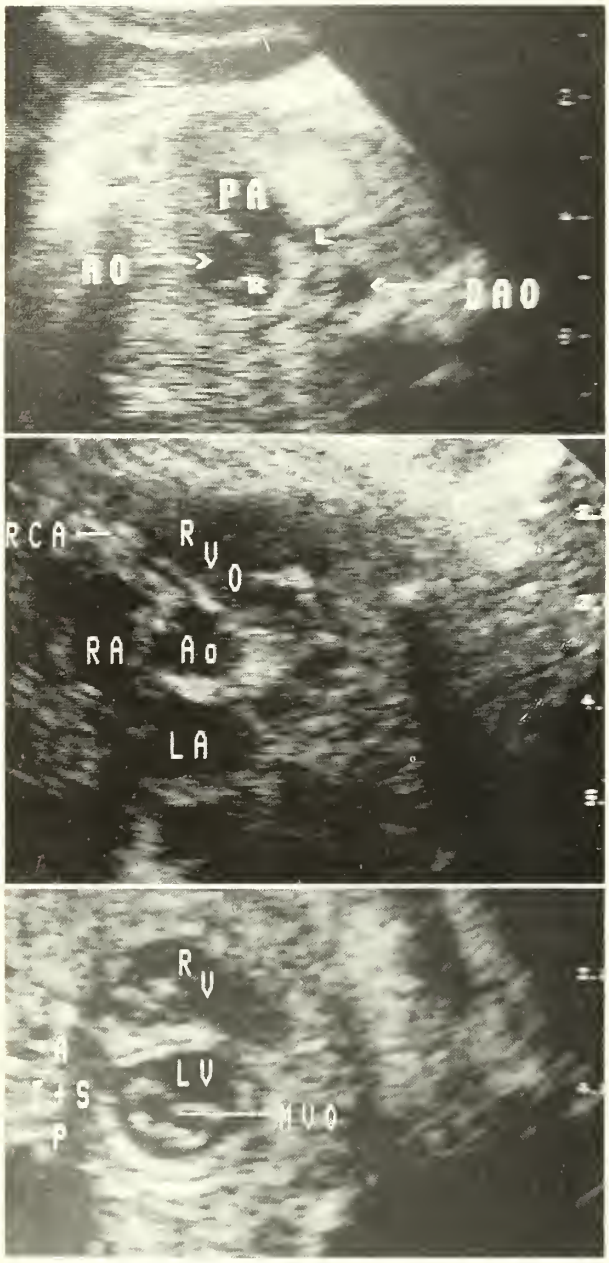

Figure 8.—**Top**, Short-axis views at the base of the heart show the aortic root (**AO**) and the pulmonary artery (**PA**) with its bifurcation into the right (**R**) and left (**L**) pulmonary arteries. The descending aorta (**DAO**) is seen in cross-section behind the bifurcating pulmonary branches. **Middle**, This image is similar to a postnatal short-axis view and shows the right ventricular outflow tract (**RVO**) surrounding the aorta (**Ao**), with the right coronary artery (**RCA**) in the normal position. **Bottom**, After magnification (3×), this frame shows focus on the heart, which lies between 2.5 and 4.5 cm away from the transducer. The cardiac structures are better demonstrated than above; the left ventricle (**LV**), the mitral valve orifice (**MVO**), and the right ventricle (**RV**) can be identified (from Schmidt et al[50]). **LA** = left atrium, **RA** = right atrium, **A** = anterior, **I** = inferior, **P** = posterior, **S** = superior

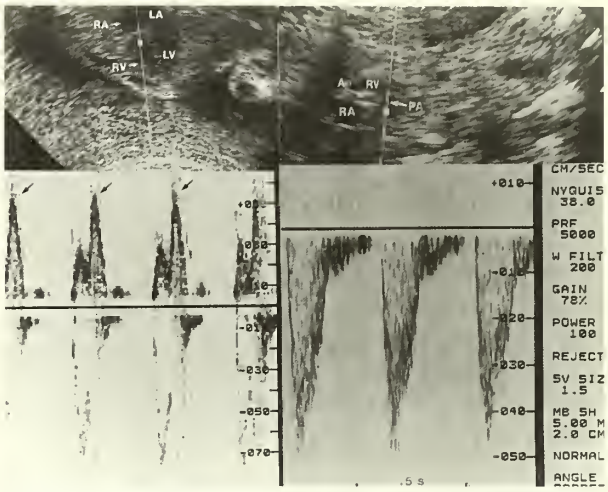

Figure 9.—A pulsed Doppler evaluation of the atrioventricular (**left**) and semilunar (**right**) valves. **Left**, The top portion shows a 4-chamber view with the sample volume (**box**) below the tricuspid valve in the right ventricle (**RV**). The spectral display (**bottom**) shows a normal Doppler signal. The signal is biphasic with a large a wave (**arrows**) due to atrial contraction preceded by a smaller v wave due to rapid filling. The mirror image below the baseline is an artifact. **Right**, Pulmonary artery (**PA**) evaluation is done from the short axis, which also shows the aorta (**Ao**), right atrium (**RA**), and right ventricle (**RV**). The sample volume (box) is always distal to the valve and here is in the main pulmonary artery. The spectral display shows a classic arterial Doppler signal-pulsatile flow with a small amount of diastolic flow (from Schmidt and Silverman[48]).

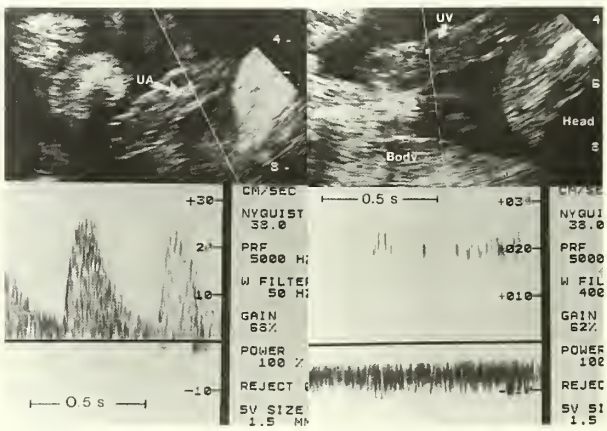

Figure 10.—A pulsed Doppler interrogation of the umbilical cord also provides important hemodynamic information. **Left**, The Doppler sample volume lies within the umbilical artery (**UA, arrow**). In the lower panel, a characteristic umbilical arterial signal is displayed above the baseline showing flow toward the transducer. **Right**, The Doppler sample volume is within the umbilical vein (**UV, arrow**); the fetal body and head are also seen. In the lower panel, a Doppler signal of uniformly low velocity throughout systole and diastole is demonstrated below the baseline. The blank space between the baseline and Doppler signal is the result of a high wall-filter setting (from Schmidt and Silverman[48]).

M-Mode Echocardiography

M-mode echocardiography in the fetus is particularly useful for defining cardiac arrhythmias and for measuring cardiac dimensions and wall thicknesses[18-24,45,46] (Figure 11). It is done using a real-time–directed beam to ensure the accurate assessment of wall and valve motion.

Findings

Detection of Fetal Heart Abnormalities

We found a structural cardiac abnormality in 135 (9%) cases among more than 1,500 fetal examinations (Table 1). Isolated cardiac rhythm disturbances were present in 17%.

Atrioventricular septal defect (atrioventricular canal defect) was the commonest serious structural abnormality we found (Figure 12). This defect often was part of a complex cardiac lesion that included left atrial isomerism, complete heart block, and nonimmune hydrops or in association with chromosomal abnormalities. In all, 85% died either in utero or during the neonatal period.

Ventricular septal defects were found as isolated phenomena as frequently as were atrioventricular septal defects (Figure 13) (Table 1). We have observed apparent spontaneous closure of a ventricular septal defect on two follow-up examinations when the lesion was an isolated phenomenon. An isolated ventricular septal defect may be difficult to detect because interventricular shunting is minimal and bidirectional as a result of similar ventricular pressures (Figure 13).

We have encountered nine cases of cardiomyopathy, more often with dilated, poorly contracting ventricles and atrioventricular valve regurgitation associated with fetal hydrops.[58] One fetus presenting with hypertrophic cardiomyopathy was identified to have the Noonan syndrome at birth. Two fetuses appeared to have normal cardiac function at 20 weeks' gestational age, but were found to have dilated cardiomyopathy shortly after birth, suggesting that it is a difficult disease to diagnose prenatally and that myocardial dysfunction may occur either after examination in utero or after birth as in some of our observations.

Several forms of complex cardiac defects that involve a single functioning ventricle have been detected. Most commonly this is in a hypoplastic left heart complex with aortic or mitral atresia (Figure 14).[59] Although the classic case of the absent left ventricle is usually an uncomplicated diagnosis, variants of this lesion may present diagnostic and management dilemmas. These include fetuses with a small left ventricle, endocardial fibroelastosis, and

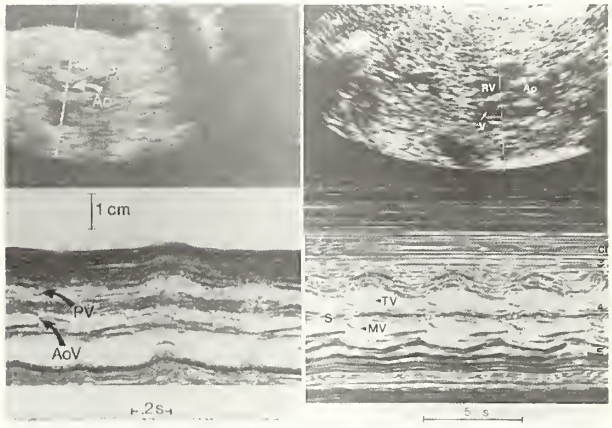

Figure 11.—Real-time–directed M-mode ultrasonogram allows an assessment of the timing of atrial and ventricular events. **Left,** In the top frame, the M-mode cursor has been passed through the fetal thorax, the pulmonary artery **(PA)** and its valve, the aorta **(Ao)** and its valve **(arrows)**, and the left atrium posteriorly. The bottom frame shows the opening of the aortic valve **(AoV)** and the pulmonary valve **(PV)** within their respective ventricles. The left atrium and the corresponding atrial contraction can be seen by the changing size of the left atrium as contributed to by the left atrial wall contraction. **Right,** In the top frame the M-mode cursor line crosses the right **(RV)** and left ventricle **(LV)** seen in long axis. In the bottom frame, the M-mode recording shows normal movement of both ventricular walls in systole. Tricuspid **(TV)** and mitral valve **(MV)** motion is also seen. The ventricular septum **(S)** and both ventricular free walls have about the same thickness (from Schmidt and Silverman[48]).

TABLE 1.—*Cardiac Structural Abnormalities and Survivors After Fetal Ultrasonography (N > 1,500)*†*

Abnormality	*Percent of Total*	*Survivors, % of Defects*
Atrioventricular septal defect, including 4 with left atrial isomerism and CHB	1.5	18.2
Ventricular septal defect (VSD), including 1 with left atrial isomerism and CHB	1.5	45.5
Cardiomyopathy, including 3 with familial disease	0.9	28.6‡
Pulmonary atresia or stenosis without VSD	0.8	33.3
Double-outlet right ventricle, including 1 with pulmonary stenosis	0.7	0
Hypoplastic left heart syndrome	0.7	0
Univentricular atrioventricular connection, 3 left-sided, 1 right-sided	0.5	0
Ebstein's anomaly	0.4	0
Aortopulmonary transposition with VSD	0.3	0
Truncus arteriosus tetralogy of Fallot	0.3	0
Multiple rhabdomyoma	0.3	50.0
Thoracopagus	0.4	0
Others	1.1	37.5
Total	9.4	

CHB = complete heart block

*From Silverman.[15] †Based on data available in 1988. ‡One after heart transplant at 6 months of age.

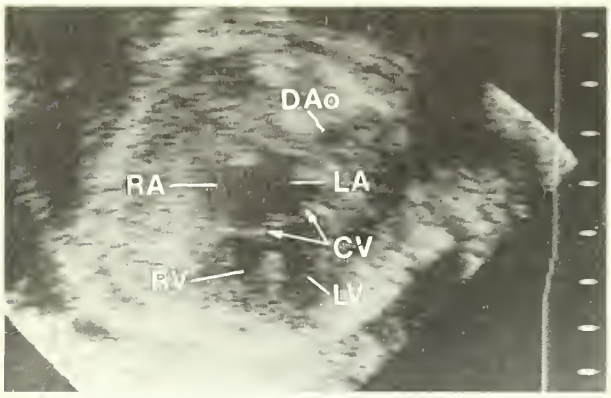

Figure 12.—This example of a 4-chamber view of a fetus with an atrioventricular septal defect shows the common atrioventricular valve (CV) straddling the left and right atria (LA, RA) and the left and right ventricle (LV, RV). The fetus was 18 weeks' gestation at the time the image was made (from Schmidt and Silverman[48]). DAo = descending aorta

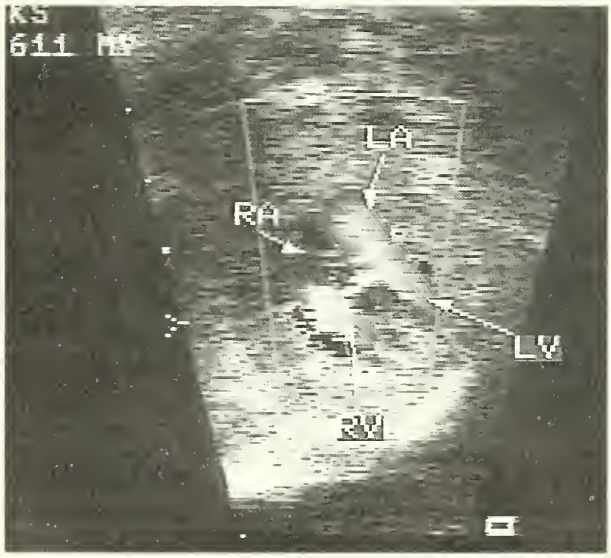

Figure 13.—A 4-chamber view of a ventricular septal defect is shown. The right atrium (RA), right ventricle (RV), left atrium (LA), and left ventricle (LV) can be seen lying within the fetal thorax. The Doppler color flow information is represented in black and white, but clearly shows flow between the two ventricles related to a ventricular septal defect.

a dysplastic, immobile aortic valve or with a nearly normal left ventricle but with poor ventricular function, mitral regurgitation, and severe endocardial fibroelastosis. We have seen three cases of mitral valve stenosis or atresia and one with Shone's complex (parachute mitral valve, a single left ventricular papillary muscle, bicuspid aortic valve, and atrial and ventricular septal defects). One fetus died prenatally, and another was born with the CHARGE* association and died at 3 months. In addition, we have seen five fetuses with a single atrioventricular connection. Three had an absent left atrioventricular connection, with a double-outlet right ventricle and arch

*The CHARGE association is a complex of defects including Coloboma, Heart defects, choanal Atresia, mental Retardation, and Genital and Ear anomalies.

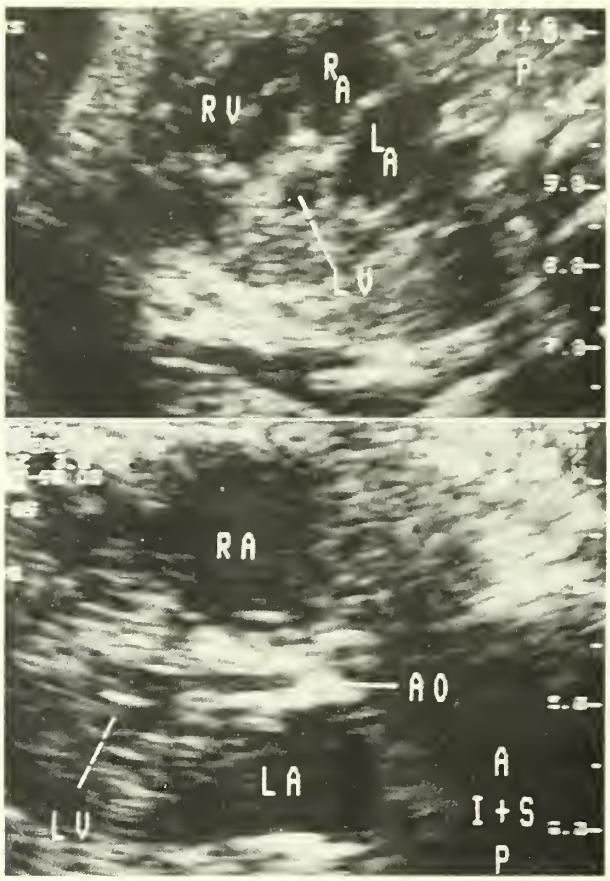

Figure 14.—A view of a hypoplastic left heart was taken in a patient at 30 weeks' gestation and referred because the obstetrician had noted an enlarged left atrium. The top frame, taken in a 4-chamber view, shows a minute left ventricle (LV) with a thickened endocardium. The other chambers, right atrium (RA), right ventricle (RV), and left atrium (LA), can be identified. In the bottom frame, in an equivalent to a parasternal long-axis view, the minute left ventricular outflow tract and hypoplastic ventricle are identified. There appears to be no continuity between the aorta (Ao) and the left ventricle (from Schmidt and Silverman[49]).

anomalies, whereas one had an absent right atrioventricular connection and transposition. None of these infants survived beyond the first month of life.

Various forms of right heart abnormalities can be diagnosed. We have seen eight patients with severe pulmonary valvar obstruction, either critical stenosis or atresia (Figure 15) (Table 1). Although postnatally these patients frequently have a small right ventricle, it may be larger than normal during early gestation.[60,61] Tricuspid regurgitation is always seen in these patients. Ebstein's anomaly of the tricuspid valve has been seen in seven patients (Figure 16). None survived the first week of life, with two dying in utero.[62,63] Significant risk factors have been seen frequently. One was the child of a woman with Ebstein's anomaly, one of a woman receiving large doses of lithium,[64] and one of a woman with diabetes mellitus; the last fetus also had skeletal anomalies.

Defects in the ventriculoarterial connection are not unusual. We have seen four fetuses with transposition of the great arteries and ventricular septal defect. Two had

associated systemic malformations, namely omphalocele and diaphragmatic hernia. Truncus arteriosus was seen in three fetuses. One of these also had trisomy 13.[65] One has survived to undergo surgical correction after delivery. A total of 13 fetuses with forms of tetralogy of Fallot have been seen, including 7 with a double-outlet right ventricle and 2 with an absent pulmonary valve complex. These lesions have a higher rate of recurrence within families than other lesions; three of four fetuses with standard tetralogy of Fallot had immediate relatives with the same abnormality. They are also frequent in fetuses with midline anomalies, including diaphragmatic hernia, omphalocele, cleft lip and palate, holoprosencephaly, or ectopia cordis (Figure 17).

In each of three fetuses we have seen with thoracopagus, we could identify the major but not complete aspects of the disorder.[66,67] All have had major abnormalities and fusion at the ventricular level inconsistent with postnatal survival. The one woman who refused termination required a cesarean section for delivery of twins, who died shortly after birth.

Three cases of rhabdomyoma as an expression of tuberous sclerosis were encountered (Figure 18). Hydrops, occasionally found in these cases, may be related to hamartomas obstructing venous return or ventricular inflow.[68] A lesion in the ventricular septum in one fetus produced left ventricular outflow obstruction and left ventricular endocardial fibroelastosis. These lesions are the only prenatal expression of tuberous sclerosis; therefore, detection provides an important basis for the genetic counseling of parents who carry this gene.

Valvar stenosis can be readily identified in utero. Flow disturbance imaged with color flow mapping and

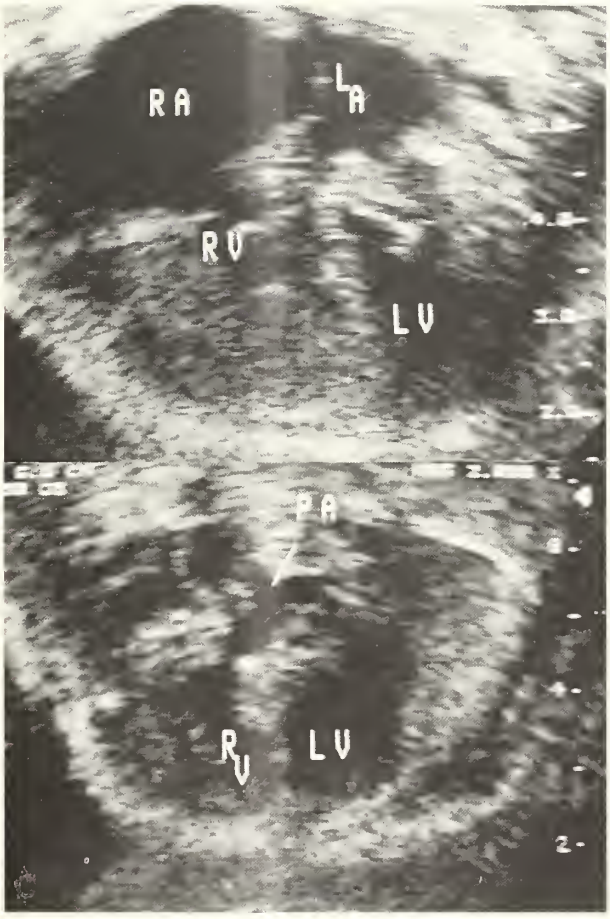

Figure 15.—In the top frame, taken in a 4-chamber view, the intense hypertrophy of the right ventricle (RV) and the right ventricular myocardium can be identified. The pericardial effusion highlights the limits of the muscle. The right atrium (RA) is enlarged and the right ventricular cavity small. In a cranially angulated 4-chamber view (bottom frame), bright echoes in the region of the pulmonary valve annulus can be identified. No forward flow was identified across the structure. The pulmonary artery (PA) bifurcation is shown. The endocardium of the ventricle appears bright (fibroelastosis) and the right ventricle appears hypertrophied (from Schmidt and Silverman[49]). LA = left atrium

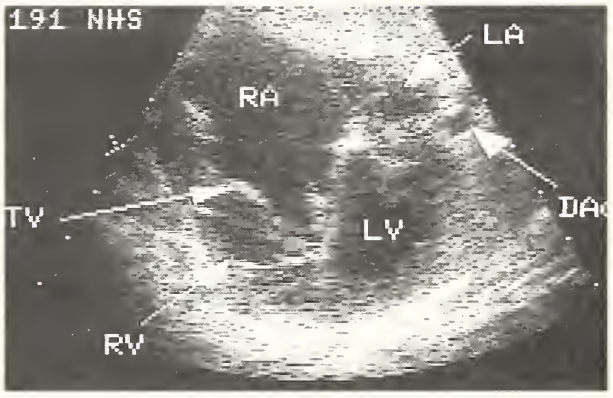

Figure 16.—Ebstein's anomaly is shown in a fetus at 30 weeks' gestation. The 4-chamber view shows a characteristic displacement of the septal leaflet of the fetal tricuspid valve (TV) and large sail-like anterior leaflet. The right ventricle (RV) appears diminished in size by the displacement of the enlarged right atrium (RA) (from Silverman, reprinted with permission[15]). DAo = descending aorta, LA = left atrium, LV = left ventricle

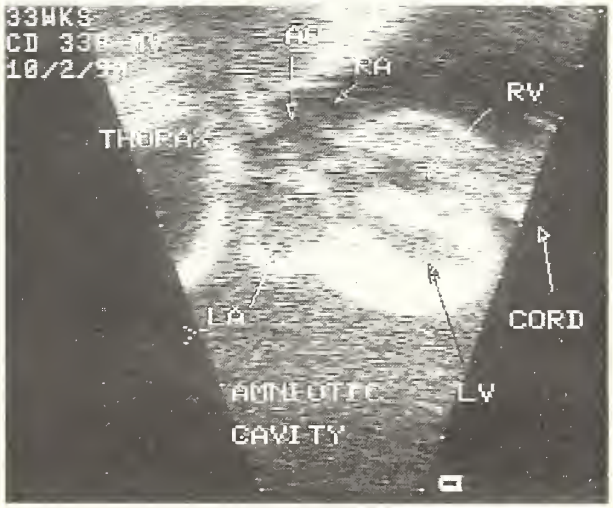

Figure 17.—A fetus is shown with ectopia cordis seen at 33 weeks' gestation. The entire heart is outside the chest wall in the amniotic cavity. All 4 cardiac chambers are seen next to the umbilical cord. In addition, there is a large superior ventricular septal defect between the right (RV) and left (LV) ventricles (from Silverman[15]). Ao = aorta, LA = left atrium, RA = right atrium

substantiated by continuous wave Doppler ultrasonography allows the gradient to be measured, even though the velocity is slow because of the low blood pressure in the fetus.

Diagnosis and Treatment of Fetal Cardiac Arrhythmias

Fetal arrhythmias are a common occurrence, with a frequency of approximately 15% in our series (Table 2).

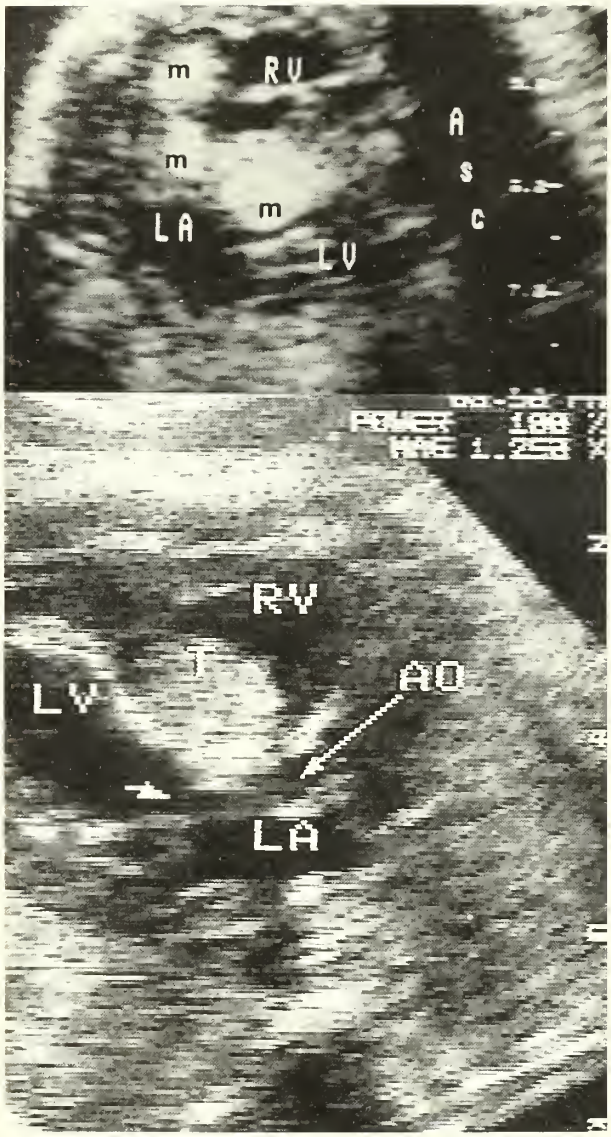

Figure 18.—Two ultrasonograms taken from a fetus with a rhabdomyoma show a pattern consistent with a diagnosis of tuberous sclerosis. In the top frame, the masses **(m)** appear to be in the apex, the free wall of the right ventricle **(RV)**, and protruding into the right atrium. The bottom frame shows a large tumor mass **(T)** within the ventricular septum and narrowing the left ventricular **(LV)** outflow tract. Note the brightness of the endocardium of the left ventricle, indicating endocardial fibrosis. The mass encroaches on the left ventricular outflow tract situated between the left ventricle and aorta **(Ao)**. This fetus was found to have endocardial fibroelastosis as a consequence of the left ventricular outflow tract obstruction at birth (from Schmidt and Silverman[48]). **LA** = left atrium, **LV** = left ventricle, **RV** = right ventricle

They can be difficult to diagnose because electrical events cannot be measured, only the mechanical result of these events. Therefore, the construction of ladder diagrams (Figure 19) is crucial to analyzing and understanding arrhythmias. Ladder diagrams, which allow a determination of the temporal sequence of atrial and ventricular contraction, are generally derived from M-mode or Doppler ultrasonography. Normally the atrial activity is followed by that of the atrioventricular node, which in turn is followed by contraction of the ventricle.

The most common arrhythmia seen in fetuses is isolated premature atrial contractions, accounting for two thirds of the arrhythmias in our series (Table 2). M-mode (Figure 20) or Doppler ultrasonograms (Figure 21) can easily see these premature beats. Premature atrial contractions are benign, usually transient, and do not require treatment.[18-24] Because caffeine, nicotine, chocolate, and other pharmacologically active substances can increase their frequency, abstinence from these is usually recommended. Isolated premature atrial contractions rarely progress to supraventricular tachycardia. Therefore, periodic monitoring of the fetal heart rate by the primary physician is essential, but repeat fetal echocardiography is rarely indicated.

Isolated premature ventricular contractions were much rarer than atrial contractions in our experience, but others have found them more frequently.[23] Differentiating atrial from ventricular premature beats can be difficult in a fetus. The most reliable method involves measuring the compensatory pause. The compensatory pause is a phenomenon seen in electrocardiography, caused by the resetting, or lack of resetting, of the sinus node. A complete compensatory pause occurs when the interval from the beat before the premature beat to the one after the premature beat is equal to the interval between two normal beats. A complete pause is more commonly associated with premature ventricular contractions (Figure 22), whereas premature atrial contractions generally have an incomplete compensatory pause; that is, the interval is less than two normal beats.

Fetal tachyarrhythmias are common, accounting for 15% of all arrhythmias in our series. Most common is a supraventricular tachycardia (Figure 23). Though this may be tolerated for extended periods, it can lead to car-

TABLE 2.—*Fetal Arrhythmias Detected by Ultrasonography**

Arrhythmia	*Fetuses, No.*	*Treated, No.*	*Neonatal Survivors*
Premature atrial contraction	190	--	189
Premature ventricular contraction	3	--	3
Supraventricular tachycardia	17	16†	16
Atrial flutter	5	5‡	5
Complete heart block	19	2§	11

*From Silverman.[15]

†Effective treatment: digoxin alone in 11, digoxin and verapamil in 2, flecainide in 2, and digoxin and procainamide hydrochloride in 1.

‡Effective treatment with digoxin alone in all except 1 fetus, controlled with digoxin, quinidine sulfate, and verapamil.

§In 1 fetus with heart block, fetal placement of a pacemaker was only successful for a short time, and the fetus died during the operation.

diac failure, fetal hydrops, and fetal demise. Stroke volume is usually decreased during tachycardia; this can be seen by examining the Doppler signal in the umbilical cord (Figure 24). Atrial flutter usually presents with varying degrees of atrioventricular block (Figure 25) and also with hydrops due to cardiac failure.

The treatment of tachyarrhythmias depends on the age of the fetus. The preferred course is to deliver the fetus because treatment is much safer and more reliable after birth. If delivery is not indicated because of other factors, intrauterine treatment may be required. Medication administered to the fetus by giving it to the mother usually is effective[18,19,26,69-71] and therefore is the treatment modality of choice. Direct administration to the fetus is rarely indicated.

Digoxin has been the drug of first choice.[18,19,70-72] If it fails to convert the fetal heart rate to sinus rhythm, we additionally use flecainide acetate, verapamil, propranolol

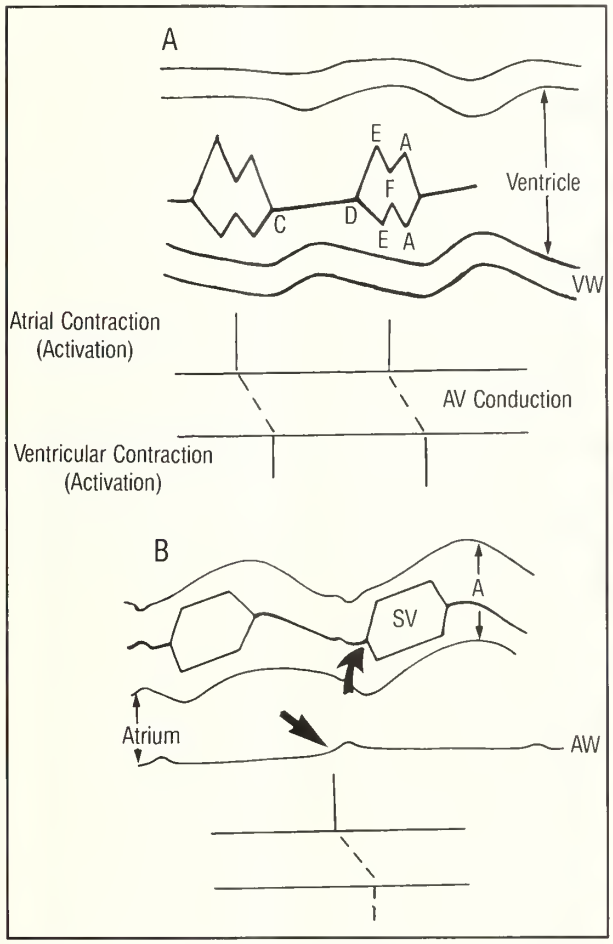

Figure 19.—The schematic representation shows the motion of cardiac structures that may be seen by M-mode echocardiography and ladder diagrams obtained from these recordings. **A,** This depicts the ultrasound beam passing through a ventricle and an atrioventricular (**AV**) valve within it. The atrioventricular valve leaflets can be seen opening in early diastole (D-E portion), moving towards each other in mid-diastole (E-F), and moving away from each other again in late diastole during atrial contraction (F-A). The beginning of this second opening (F point) indicates the onset of atrial contraction. The closure of the valve leaflets (C point) or the beginning of forward motion of the posterior ventricular wall (**VW**) indicates the onset of the ventricular contraction. The ladder diagram (below) marks these events; the delay between atrial and ventricular activation is the atrioventricular conduction time. **B,** This shows the ultrasound beam passing through the root of a great artery (**A**), in this case the aorta and the semilunar valve within it, then through an atrium behind that vessel. The M-mode recording shows the onset of forward motion of the atrial wall (**AW; lower arrow**), which defines the beginning of atrial contraction. The opening of the semilunar valve (**SV, curved arrow**) defines the beginning of the ventricular contraction. The ladder diagram (below) demonstrates these events as in A (from Schmidt and Silverman[48]).

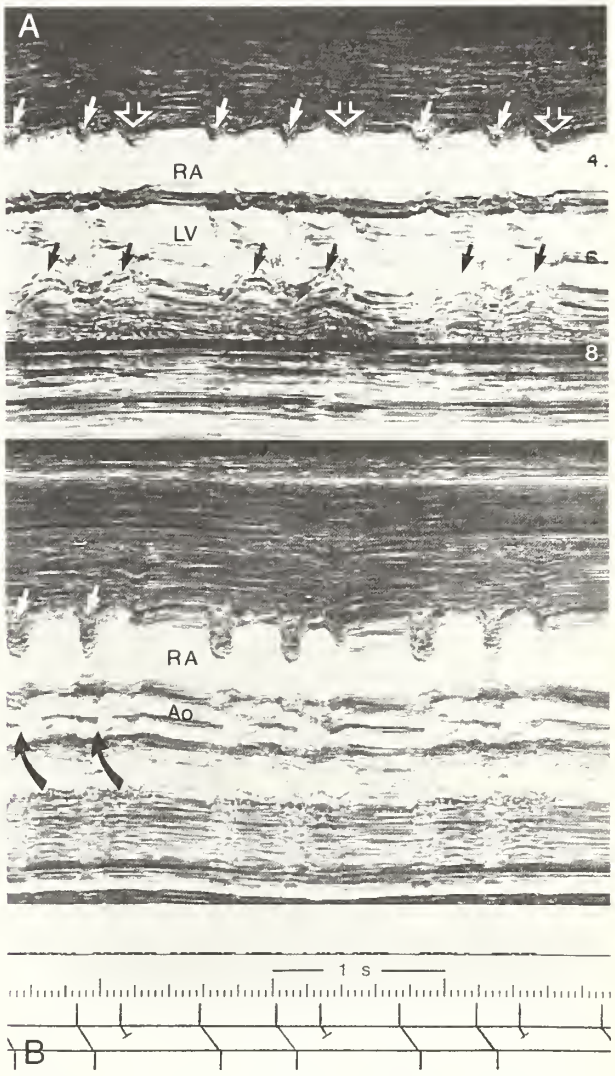

Figure 20.—An M-mode evaluation is shown in a fetus with premature atrial contractions. **A,** In the top frame, the ultrasound beam passes obliquely through the heart and shows the right atrium (**RA**) and left ventricle (**LV**). Normal atrial beats (**white arrows**) are followed by ventricular contraction (**black arrows**), but the ectopic beats (**open arrows**) do not result in ventricular contraction. The bottom frame confirms that the ectopic beats are blocked. Normal atrial contractions (**white arrows**) are followed by aortic valve opening (**black arrows**), but the ectopic beats are not. **B,** The ladder diagram shows the schematic representation of blocked premature atrial contractions. The top line is the atrium, the middle the atrioventricular node, and the bottom the ventricle (from Schmidt and Silverman[49]).

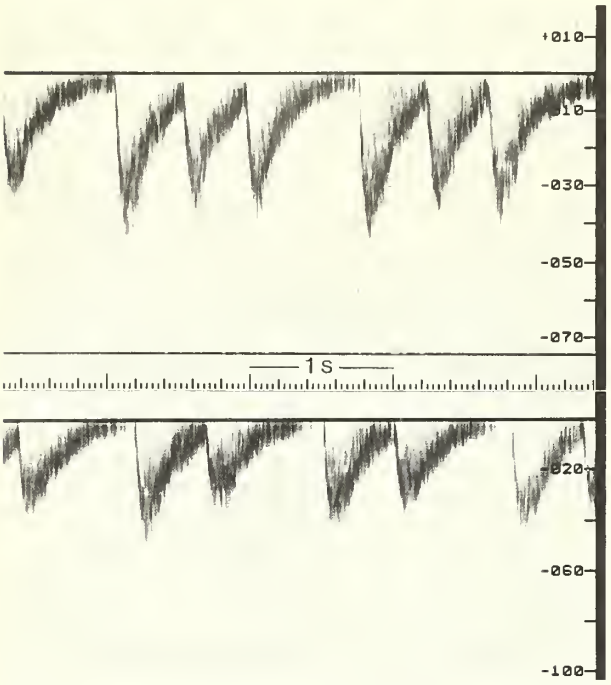

Figure 21.—An example of group beating is shown associated with premature atrial contractions as seen from the umbilical cord artery. In the top row, the group beating appears to be three beats followed by a pause and three beats followed by a pause; in the lower panel, it is two beats followed by a pause and two beats followed by a pause. The premature atrial contraction is ineffective at creating a contraction that allows umbilical arterial pulsation, identified as a pause. What is clear, particularly from the top tracing, is that the pause is an incomplete compensatory pause and therefore is a supraventricular premature contraction.

hydrochloride, or procainamide hydrochloride, in that order (Table 2). The dosage schedule for these drugs has been formulated based on loading doses for the conversion of cardiac arrhythmias in adults (Table 3). Antiarrhythmic drugs are administered intravenously in a delivery room, except for digoxin, which may be given orally. Rapid obstetrical intervention, if needed, should be conveniently located and available. During such cardioversion, the fetal heart should be directly monitored using echocardiography. During pregnancy, enteral absorption of digoxin may be limited, and additional administration of other drugs such as verapamil may decrease its clearance[69]; therefore, maintenance therapy should be controlled by monitoring maternal serum concentrations. Other drugs have been successful for converting supraventricular tachycardia.[71] Except for digoxin, treatment is best administered in a tertiary-care facility with complete support personnel because side effects for the mother or fetus may result.

Several mechanisms, including the frequent occurrence of nonconducted premature atrial contractions, group beating, or complete heart block, may lead to prolonged fetal bradyarrhythmia. We have observed group beating with bradycardia and junctional or ventricular escape beats. Doppler ultrasonography is valuable for distinguishing these conditions.

Heart block can be recognized using M-mode echocardiography, Doppler ultrasonography, or even Doppler color flow mapping (Figure 26). In 15% of our cases with fetal arrhythmia, bradyarrhythmia due to complete heart block was present. Structural heart defects are more common in fetuses with complete heart block, particularly when nonimmune hydrops is present, but heart block can be an isolated finding. Isolated complete heart block usually occurs in women with autoimmune connective tissue disease. Certain antibodies (anti-Ro[SS-A] and anti-La[SS-B]) can cross the placenta and have been found in affected newborns.[42,72] The prognosis in patients with isolated heart block, with or without documented autoimmune disease, is fair. Many fetuses can survive to delivery without serious hydrops. Those with associated congenital heart disease, however, almost invariably die of hydrops in utero or shortly after birth.

There is currently no effective therapy for infants with symptomatic heart block. Variable results have been reported with the β-agonists ritodrine and terbutaline sulfate. We were once able to raise the heart rate from 47 to 57 beats per minute in a 27-week fetus and continue the

TABLE 3.—*Dosage Schedule for Antiarrhythmic Transplacental Treatment**

	Loading		*Maintenance*			*Plasma Level*	
Drug	*Dose, mg*	*Route*	*Dose, mg*	*Route*	*Interval, hr*	*Therapeutic*	*Toxic*
Digoxin	0.5 (initial) + 0.25 q 6 hr†	Intravenous	--	--	--	--	--
	or						
	1.5-2 (in 24-48 hr)	Oral	0.25-0.75	Oral	24	1-2 ng/ml	>2.5 ng/ml
Verapamil‡§	0.1-0.2/kg	Intravenous‖	80-120	Oral	6-8	80-300 ng/ml	>300 ng/ml
Propranolol HCl	0.1-0.2/kg	Intravenous	10-40	Oral	8-6	50-100 ng/ml	--
Procainamide HCl	15/kg#	Intravenous¶	0.5-1.0 grams	Oral	4	3-6 μg/ml	>8 μg/ml
Quinidine sulfate	--	Oral only	0.3-0.4 grams	Oral	6-8§	2-6 μg/ml	>8 μg/ml
Flecainide acetate	--	--	100-150 2x/d		To add		

HCl = hydrochloride

*From Silverman.[15]
†Total: 1.25 to 1.5 mg.
‡Do not use verapamil and propranolol HCl at the same time!
§Atropine sulfate, 0.5 to 1 mg, should be on hand for managing the side effect of maternal or fetal bradycardia due to atrioventricular block.
‖Should be given over a period of 1 to 2 minutes.
¶As infusion, about 50 mg per minute.
#Maximum of 1 gram.

pregnancy to 36 weeks. After birth a permanent pacemaker was successfully implanted. Direct fetal pacing using an amnioscope has been unsuccessful at preventing fetal demise.[73] The fetal treatment group at the University of California, San Francisco, has developed and tested direct fetal pacing, placed through a hysterotomy, in animals. It has been attempted in one fetus with hydrops and a heart rate of 48 beats per minute. The fetus, however, had poor cardiac function and atrioventricular valve regurgitation before the operation and died during implantation of the pacemaker, despite capture and an increase in the heart rate. Indications for such an invasive treatment would be a heart rate of less than 55 beats per minute with hydrops fetalis and the absence of congenital heart disease.

In the overall assessment of fetal arrhythmias, isolated irregular beats are of little concern. Irregular beats associated with runs of tachycardia or bradycardia are of more concern, and a heart rate of more than 200 or less than 80

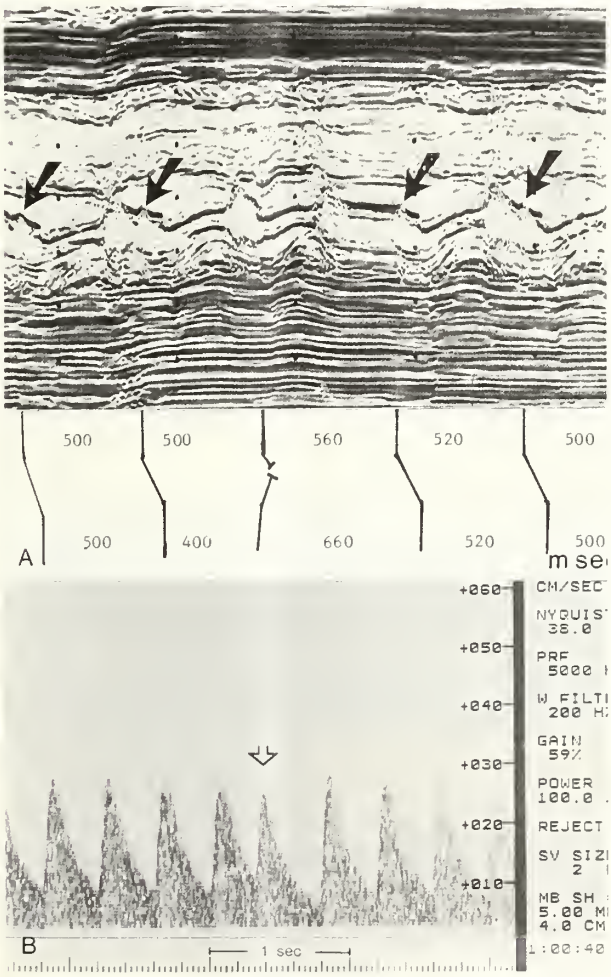

Figure 22.—An M-mode evaluation is shown in a fetus with premature ventricular contractions. **A**, The mitral valve movement and that of the left ventricular posterior wall can be seen. Normal beats are preceded by an atrial kick seen on the mitral valve echo **(arrows)**; the premature third beat has no atrial kick. In addition, the subsequent beat is delayed, resulting in a complete compensatory pause, because 2 intervals of regular beats also last about 1,020 mseconds as seen in the ladder diagram between sections. This favors the diagnosis of a ventricular contraction. **B**, A pulsed Doppler ultrasonogram was done within the umbilical artery in a different fetus and shows the hemodynamic consequence of premature beats. The premature beat **(open arrow)** has a smaller stroke volume and is followed by a complete compensatory pause; therefore, it is more likely to be of ventricular origin (from Schmidt and Silverman[49]).

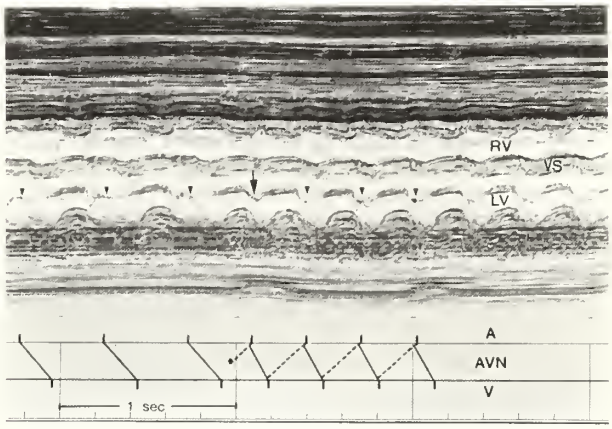

Figure 23.—An M-mode recording is shown of a 30-week fetus with a supraventricular tachycardia. This example demonstrates the reentry mechanism of the tachycardia. To the left of the recording is normal sinus rhythm; note that the atrial kick **(small black arrowheads)** on the mitral valve echo indicating atrial contraction is fairly separated from the preceding valve movement during early diastolic filling. After 3 regular beats, a premature atrioventricular nodal depolarization causes retrograde atrial and antegrade ventricular activation, thus starting a reentry cycle. The first atrial kick on the mitral valve echo appears at the same time as the early diastolic filling deflection **(large black arrow)**; during the tachycardia it then can be seen in a different position located closer to the early filling wave than during sinus rhythm (from Schmidt and Silverman[49]). **A** = atrial contraction, **AVN** = atrioventricular node activation, **LV** = left ventricle, **RV** = right ventricle, **V** = ventricular contraction, **VS** = ventricular septum

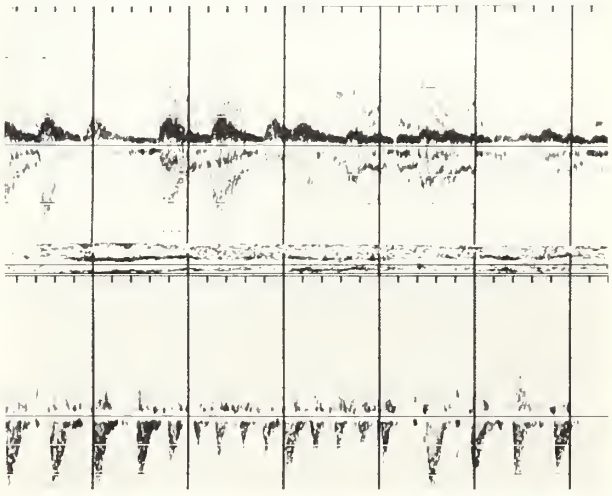

Figure 24.—A pulsed Doppler interrogation within the umbilical artery **(top)** and the pulmonary artery **(bottom)** is shown taken of a fetus with supraventricular tachycardia. The reduction in stroke volume during tachycardia, followed by a pause and resumption of normal sinus rhythm, is clearly seen in the lower panel. Horizontal lines represent Doppler velocities of 0.25 per millisecond; vertical lines are time markers (1 sec) (from Schmidt and Silverman[48]).

beats per minute requires further evaluation. Structural heart disease in patients with isolated irregular beats or with tachycardia is not as common as in patients with complete heart block.

Discussion

Outcome After Fetal Echocardiography

Our series (Table 1) confirms that the overall outcome of a fetus with a structural cardiac abnormality is unfavorable.[10,13,27,38,60,74] Eight pregnancies were terminated electively, two because of severe fetal cardiac defects, the others because of chromosomal abnormalities. There were 30 fetal or neonatal deaths, 4 fetuses are not yet born, and only 11 children (23%) were alive at the end of the neonatal period. Of the 11 infants, 4 underwent a cardiac operation within the first months of life, including 1 who had cardiac transplantation. In those cases presenting with nonimmune hydrops and cardiac defects, the incidence of fetal death was high (16 of 18 cases). Ten of these fetuses had severe atrioventricular regurgitation, and all died either before birth or within the first week of life. Eight fetuses had cardiac defects coupled with complete atrioventricular block, seven of which died prenatally or in the neonatal period. The prognosis for fetal survival appears poor in the presence of structural abnormalities coupled with atrioventricular valve regurgitation, complete heart block, or fetal hydrops. The reader should note that because fetal cardiac ultrasonography is in its early stages of development, those defects most likely to be symptomatic are more likely to have been recognized.

In the large series published by Smythe and co-workers involving 3,016 fetuses, 170 were found to have heart disease.[38] Of the 170 fetuses, 55 (32%) had major extracardiac malformations and 45 (26%) had chromosomal abnormalities. Elective termination was chosen by 77 (45%) of these patients. Of the 93 continuing pregnancies, 15 (16%) resulted in a stillborn and 43 infants (46%) died postnatally. In the cases of nonimmune hydrops with a cardiac basis, all proved fatal. In all, 35 (38%) of the 93 continuing pregnancies survived. This group found, as did our group, that the spectrum of cardiac anomalies presenting before birth was different and more severe than the spectrum that presented after birth and that the outcome of the pregnancies was less favorable than for a group of infants with heart disease occurring postnatally. Presumably this relates in some way to the reasons for the referral for an echocardiographic examination, including the high incidence of chromosomal and extracardiac abnormalities, that may also adversely affect the cardiac outcome of these children.

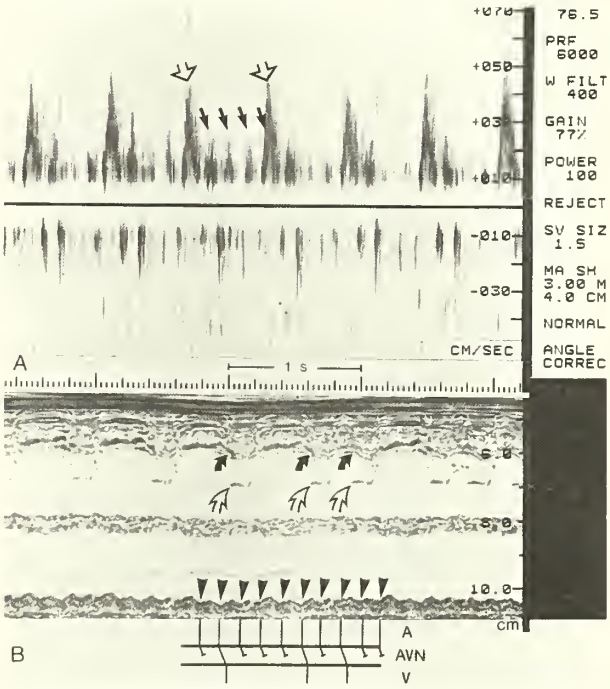

Figure 25.—Atrial flutter with atrioventricular block is shown in a 36-week fetus. **Top,** Pulsed Doppler interrogation with the sample volume placed in the descending aorta and the left atrial wall demonstrates atrial contractions (smaller flow signals, **small black arrows**) and ventricular contractions (bigger flow signals, **open arrows**). In this recording there is constantly a 4:1 atrioventricular block. This results in an apparently regular heart rate of about 100 per minute. **Bottom,** An M-mode recording from the same fetus shows rapid atrial contractions with a rate of 400 beats per minute (**black arrowheads**). Ventricular activation is inferred from either tricuspid valve closure (**open arrows**) or the onset of ventricular wall motion (**black arrows**). The ladder diagram demonstrates the presence of 4:1 atrioventricular block on the left side with one following beat showing a 2:1 block. These varying degrees of atrioventricular block result in an irregular heart rate (from Schmidt and Silverman[48]). **A** = atrium, **AVN** = atrioventricular node, **V** = ventricle

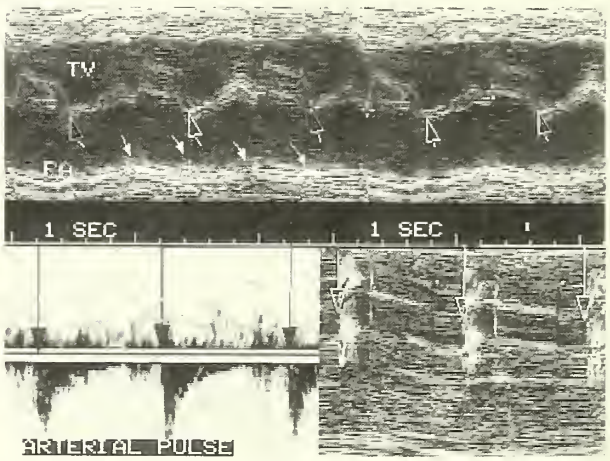

Figure 26.—A composite collection of methods is shown for recognizing complete heart block. **Top,** An M-mode strip is shown through the right ventricular wall anteriorly, the tricuspid valve (**TV**) in the middle, and the right atrial wall (**RA**) posteriorly. The scale markers indicate 1-second large divisions and 0.2-second small divisions from the opening of the tricuspid valve (**large open arrows**). The ventricular rate can be assessed at 55 beats per minute. The contractions shown on the atrial wall (**small closed arrows**) indicate a rate of 150 beats per minute. This atrioventricular dissociation indicates complete heart block. **Bottom left,** A Doppler recording from the pulmonary artery confirms the slow ventricular rate at 55 beats per minute. The arrows indicate the onset of ejection. **Bottom right,** A Doppler color flow M-mode tracing is done through the pulmonary valve. The Doppler color flow information is shown in black and white, but indicates the onset of ventricular flow (**open arrows**) at the same rate.

In one instance, the administration of betamethasone to improve the lecithin-sphingomyelin ratio caused a dramatic resolution of a serous effusion in heart block related to collagen vascular disease. Such a resolution would indicate these effusions were not on the basis of cardiac failure, but rather were a further expression of the effect of the transplacental antibodies.

Diagnostic Errors

Despite the resolution of current ultrasound equipment, errors in interpretation are possible. In our series, we made the false-negative diagnosis of a structurally normal heart in four fetuses: one each with a ventricular septal defect, aortic coarctation coupled with double-orifice mitral valve, mild pulmonary stenosis, and situs inversus (mirror-image dextrocardia). The last error, made early in our experience, should not be made if the correct position of the heart in the chest is determined first; subsequent cases of situs inversus in our series have been correctly recognized prospectively. In complex cardiac defects, the main lesion may be recognizable, but unless careful attention is paid to the entire examination, secondary lesions might be missed. In general, experience suggests that prenatal findings in complex congenital abnormalities tend to underestimate the spectrum of abnormalities.

Both false-negative and false-positive findings have been reported previously.[10,11,17,74] We found that most of the serious errors were made when using older equipment that had poorer resolution, when magnification was not possible, and when the Doppler technique was not used. Errors unrelated to equipment and beyond the ultrasonographer's control include such technical factors as suboptimal imaging, which occurs with gross maternal obesity, polyhydramnios, or unfavorable fetal positioning. The resolution of echocardiographic imaging is limited to distances of 1.0 to 1.5 mm, which may make imaging structural abnormalities such as relatively small ventricular septal defects technically impossible. Mild aortic or pulmonic stenosis may be difficult to detect, because valve structural features may not be resolved accurately enough to determine minor valve abnormalities, and blood flow velocity may be lower than after birth due to low ventricular pressures present in fetal life. Other defects such as mild aortic coarctation[75,76] or a secundum atrial septal defect may be indistinguishable from normal anatomy in a fetus. Furthermore, cardiac lesions may develop or worsen later in pregnancy, as we have observed in cases of cardiomyopathy, and will be detected only if serial studies are done. We have made it a practice to restudy fetuses later in gestation when there is doubt as to whether the study is normal. On the other hand, some lesions may disappear on subsequent studies, such as ventricular septal defects that close spontaneously.

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Preimplantation Diagnosis

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Preimplantation embryonic biopsy and analysis offer couples at increased risk of having offspring affected with a genetic disorder the possibility of an early prenatal diagnosis. For many couples, this approach would avoid the issue of the selective termination of affected fetuses. Substantial advances have been made in the area of preimplantation diagnosis, but the possible difficulties with this approach cannot be ignored.

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The prenatal diagnosis of genetic disease currently allows at-risk couples the option of having only unaffected offspring. To achieve this goal, they are faced with terminating a pregnancy if an affected offspring is diagnosed. Traditional prenatal diagnosis is performed by midtrimester amniocentesis at 15 to 16 weeks' gestation and provides a diagnosis from one to five weeks after the procedure. This necessitates a second-trimester termination procedure if a couple wishes to abort an affected fetus. Because of this, chorionic villus sampling was devised as an earlier prenatal diagnostic procedure (10 to 12 weeks' gestation). Although the possibility of a first-trimester termination procedure is more acceptable to some couples, to others neither approach provides a good option. The availability of preimplantation prenatal diagnosis would avoid the issue of pregnancy termination for many couples. With this approach, a biopsy specimen is taken of the early embryo after fertilization in vitro. This is then analyzed for the specific disorder the couple is at risk for, and only unaffected embryos are transferred.

Several approaches may be used to obtain a biopsy specimen of the developing embryo. The first is polar body analysis. This involves removing the first polar body, the nonfunctioning haploid product of meiosis I. The problem with this approach is that crossing over may have occurred between sister chromatids, resulting in difficulty in interpreting the analysis. Accordingly, the most common approach that has been used is the biopsy of a single blastomere removed from a four- to eight-cell embryo. This approach has the disadvantage of having only one cell available for analysis. Efforts are currently underway to culture these individual blastomeres to provide more cells for analysis. The third approach is trophectoderm biopsy of the blastocyst. This would provide more cells for analysis. Human embryos, however, are difficult to culture to the blastocyst stage, and implantation rates may be lower for blastocysts.

Many technical, ethical, and financial issues involved in this approach to prenatal diagnosis remain unanswered. Much work has already been done on animals as a prelude to human preimplantation diagnosis. In this review we will discuss the current methods being used for preimplantation biopsy, present an overview of the preclinical animal work, and discuss analyses that have been reported in humans.

Techniques for Preimplantation Diagnosis

Embryo Recovery

There are two ways in which embryos can be obtained for preimplantation diagnosis. Embryos that have been fertilized in vivo after timed intercourse or insemination can be obtained by uterine lavage.[1] This technique has the advantage of permitting spontaneous conception and therefore minimal technologic intervention for the parents, other than the extraction of the preimplantation embryo. One disadvantage of this approach is the low efficiency of embryo recovery, which imposes limitations on successful implantation. A second disadvantage arises from the possible failure to retrieve an embryo that may then implant and establish a pregnancy with an affected fetus.

The second strategy for obtaining embryos for preimplantation diagnosis is the application of techniques for in vitro fertilization. The fundamental procedures involved are the stimulation of oocyte maturation, oocyte retrieval, fertilization in vitro, and transfer of the unaffected embryos.

Success rates for in vitro fertilization cycles critically depend on the number of embryos available for transfer. The normal process of follicular maturation selects one of

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a cohort of available follicles for maturation and release at ovulation. To overcome that selection process and increase the recruitment of follicles, human menopausal gonadotropins are administered daily to the woman. The process is monitored by transvaginal ultrasonography, permitting the frequent assessment of the size and number of follicles developing. Criteria for an adequate response are determined by individual programs and are further modified for different patient circumstances. In general, stimulation is continued until the dominant follicles are larger than 16 to 17 mm and there are at least three follicles larger than 14 mm. Usually between 8 and 20 follicles are recruited. The serum estradiol level is used to verify the normalcy and maturity of the follicles visualized, anticipating that about 200 pg per ml per follicle greater than 14 will be secreted. When follicles are large enough, sufficient in number, and estrogen levels are appropriate, the final maturation of the oocyte is initiated by administering the luteinizing hormone-like hormone and human chorionic gonadotropin, and the oocyte retrieval is scheduled for 35 hours later.

Oocyte retrieval is usually accomplished using transvaginal ultrasonography to guide an aspirating needle, which is inserted once into each ovary from the vagina. Follicles are sequentially entered and the follicular contents aspirated and submitted to the laboratory for analysis. Each tube containing follicular fluid and granulosa cells is examined under a dissecting microscope to search for the oocyte. Overall efficiency of the process is about 66% to 75% recovery of oocytes per follicle aspirated. Although a small number will have two or more oocytes, most follicles (92%) will have one oocyte.[2]

After an oocyte is identified, maturity is assessed, either by observing the structure of the surrounding cumulus and corona cells or by nuclear assessment and visualizing polar body extrusion. Oocytes retrieved from different follicles within the same ovary may be at differing stages of maturation, with some mature, preovulatory, metaphase II, and others immature, with intact visible germinal vesicles. The oocytes will be inseminated at different times, as dictated by their stage of maturation. The insemination will occur six to eight hours after retrieval for mature oocytes and 24 to 36 hours after retrieval for immature oocytes that are matured in culture. Sperm for insemination is prepared by collecting an active motile concentrate. Most commonly this involves a process of washing and the recovery of motile sperm that swim up into a layer of media from a centrifuged pellet, but there are many different techniques for sperm preparation that can be used. When there is no known sperm dysfunction, a small volume of media containing 50,000 to 100,000 active sperm will be placed in the dish containing the oocyte. The inseminated oocytes are then cultured for 14 to 16 hours, after which evidence for fertilization can be detected by visualizing the second polar body or by identifying two pronuclei within the zygote. In most cases, 65% to 75% of the oocytes will be fertilized, with higher percentages seen with mature oocytes and less than 50% of immature oocytes expected to fertilize.

After fertilization, the zygotes are transferred to growth media and continued in culture. Healthy embryos will have divided to the four-cell stage by 48 to 56 hours after retrieval and will have achieved an eight- to ten-cell stage one day later. These embryos are then available for assessment by blastomere biopsy.

Blastomere Biopsy

The concepts and methods of blastomere biopsy have been recently reviewed extensively,[3,4] so we will only describe the biopsy methods used in recent reports of preimplantation diagnosis leading to human pregnancies[5,6] and as currently used in our program.

Embryos at the six- to ten-cell stage are transferred individually to the heated platform of an inverted microscope in a micromanipulation chamber that contains phosphate-buffered medium to control the pH and is sealed with paraffin oil to prevent evaporation. The embryo is anchored on a fire-polished suction pipette (outside diameter 200 μm) and oriented for biopsy (Figure 1). Using a small pipette containing acidified medium (pH 2.5), a fine stream is directed at the zona pellucida of the embryo until an opening dissolves.[7] Then a fire-polished biopsy pipette is moved into the hole produced by this zona-drilling procedure, and gentle suction is used to withdraw one blastomere.[8] If inspection at high power fails to reveal a nucleus in this blastomere, it is considered an anucleate fragment, and a second blastomere is removed for examination. After a successful biopsy, the micromanipulation chamber is moved to the dissecting microscope, where the nucleated blastomere is transferred to a microfuge tube for analysis. The presence of the blastomere in the tube is verified after transfer by inspection under the dissecting microscope. All such procedures are done inside a containment hood to minimize the risks of contamination.

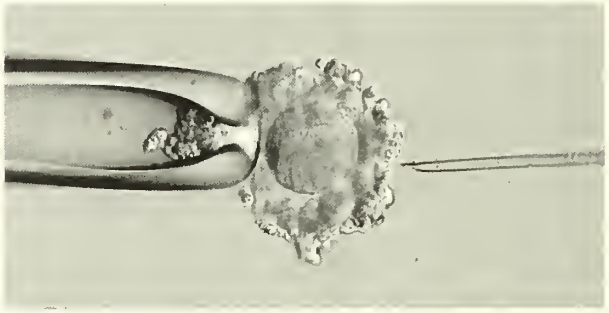

Figure 1.—The photograph shows micromanipulation of an embryo before biopsy of the blastomere.

Embryo Transfer

Embryos that survive blastomere biopsy and are determined to be unaffected can then be transferred back to the woman. This can be by either a uterine transfer, usually accomplished on the second or third postretrieval day (either four- to six-cell embryos or six- to 10-cell embryos), or a transfer into the fallopian tube. The uterine transfer is the most commonly used procedure and in-

volves the placement of a small catheter through the cervix into the uterus near the fundus. The desired number of embryos, in a small volume of about 50 μl, are layered into the uterus, with all of the embryos transferred in one procedure. For intratubal transfer, usually a laparoscopy is used to directly visualize the fimbrial end of the tube, and a transfer catheter is threaded about 3 cm into the tubal lumen. Alternatively, a catheter can be threaded transcervically into the uterus and directed into the fallopian tube for intratubal transfer. There are some advocates of intratubal transfer as a procedure offering higher probabilities of success compared with intrauterine transfer, but this is controversial. The success of implantation is then determined by the health of the embryos, and success rates are influenced predominantly by the number of embryos replaced and the age of the patient (Figure 2). Overall expectations of success for the average United States programs, without intervening manipulation of the embryos, are in the range of 18% probability of successful delivery per oocyte retrieval in women

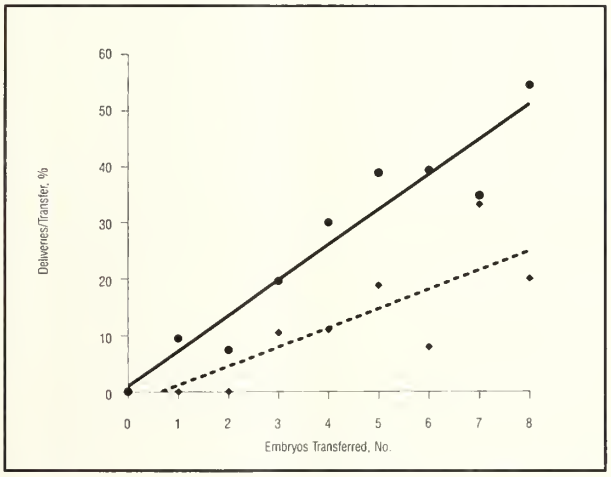

Figure 2.—The graph shows the percentage of deliveries per number of embryos transferred, University of California, San Francisco, in vitro fertilization program, 1989 to 1992. Lines are computer-derived best-fit trend lines. -◆- = women younger than 40 years, —●— = women 40 years or older

younger than 40 years. Programs in the top 10% of reporting centers, including our program at the University of California, San Francisco, have success rates in the 28% to 35% range for deliveries per oocyte retrieval in women younger than 40.

Blastomere Analysis

The polymerase chain reaction (PCR) was developed to amplify small numbers of unique gene regions from total genomic DNA using site-specific primers.[9] Beginning with the third cycle of amplification, each additional cycle logarithmically amplifies the number of unique-length target DNA sequences. Approximately 30 cycles amplify target genes about a millionfold to characterize multiple site-specific mutations from DNA obtained routinely by chorionic villus sampling or amniocentesis. About 60 cycles amplify target genes in single cells sufficiently to analyze specific mutations.[10] Because increased specificity is required for the analysis of single cells, protocols must be more robust for preimplantation diagnosis than for routine prenatal diagnosis.

The PCR mixtures routinely include the four nucleotides deoxycytidine triphosphate, deoxyguanosine triphosphate, deoxyadenosine triphosphate, and deoxythymidine triphosphate; a buffer that maintains a physiologic pH and optimizes polymerase enzyme efficiency; and a heat-resistant DNA polymerase derived from bacteria growing in hot springs, such as *Thermus aquaticus* (Cetus). This polymerase must withstand heating numerous times to 95°C to denature the DNA during each cycle (described later). Because all enzymes in bacteria growing in hot springs are heat resistant, this was a logical source from which to purify a heat-resistant polymerase. The PCR also requires cycling tubes at different temperatures for multiple cycles at controlled time periods. Automated thermocyclers accomplish this task easier, faster, and even more reliably than technicians with multiple temperature heating blocks and a stopwatch did in the original experiments.

As each human cell carries 6 billion base pairs of DNA packaged in 46 chromosomes, specifically amplifying a single locus requires synthesizing primers that recognize only one locus along with a partner that recognizes another unique locus within 2,000 base pairs. Amplifying 150 base pairs of unique target DNA among these 6 billion base pairs with an efficiency of between 55% and 70% per cycle and not detecting other sequences that give extraneous fragments is the equivalent of consistently identifying and amplifying a 1-oz needle in a 160-ton haystack. The minimum primer length expected to recognize unique sequences is at least 17 base pairs ($4^{16} = 4 \times 10^9$). In practice, primers 20 to 30 base pairs long are synthesized for routine amplifications. Because primers cannot be allowed to recognize repetitive sequences, each other, or sequences within themselves, computer programs (such as Primer, version 0.5, Whitehead Institute for Biomedical Research, 1991) have been developed to choose the optimal primer sites in sequenced DNA.

The polymerase chain reaction begins with double-stranded DNA that is denatured at 90°C to 95°C for two to five minutes to provide single-stranded target DNA (Figure 3). Although the most reliable means to generate amplifiable DNA from prenatal amniocyte or chorionic villus cell DNA is to purify the DNA before beginning (R.V.L., unpublished data, March 1992), the most reliable way to amplify DNA from a single cell is to place the cell in hypotonic solution and proceed directly to PCR, which begins with denaturing the DNA.

The temperature is lowered until the high concentration of primers can specifically anneal to identical DNA sequences. Annealing to homologous sequences is minimized because mismatches have fewer hydrogen bonds between base pairs that do not hold the primer to the target as tenaciously and may also destabilize the double-stranded molecule by suboptimal tertiary structures.

The elongation step then begins at the double-stranded stable primer or target DNA locus and synthesizes a longer complementary DNA fragment from the annealed primer. The time is chosen so that the double strand can be extended past the second primer site but not so long as to generate secondary artifacts during the many PCR cycles. This completes the first cycle with the number of target sequences doubled and the amount of total DNA practically unchanged.

The second cycle (Figure 4) again denatures, anneals, and elongates unique target DNA sequences. This step, however, now generates two unique-length DNA sequences defined by the positions of both primers. The third cycle repeats the denaturing, annealing, and elongating steps but, most important, increases the number of unique sequences from two to eight. From this step onward, the number of unique-length synthesized fragments increases logarithmically. In this way it is possible to generate more unique-length DNA than the total amount of DNA originally in the beginning tube. This unique-length DNA can be sized by acrylamide gel electrophoresis, digested by restriction enzymes to detect DNA base-pair mutations or polymorphisms,[11] or analyzed by dot blot or reverse dot blot analysis to determine target gene content.[12]

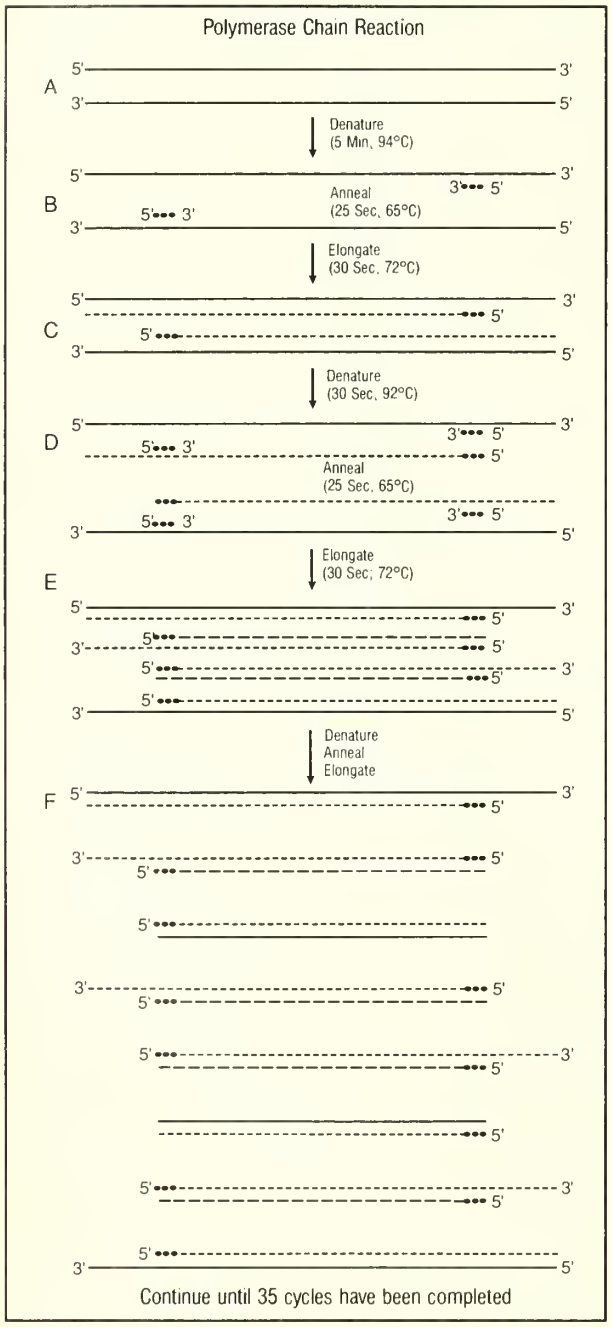

Figure 3.—A polymerase chain reaction (PCR) scheme is shown. Three complete PCR cycles amplify template sequence to 8 unique-length segments defined by primer location. Each cycle includes a denaturing, an annealing, and an elongation step.

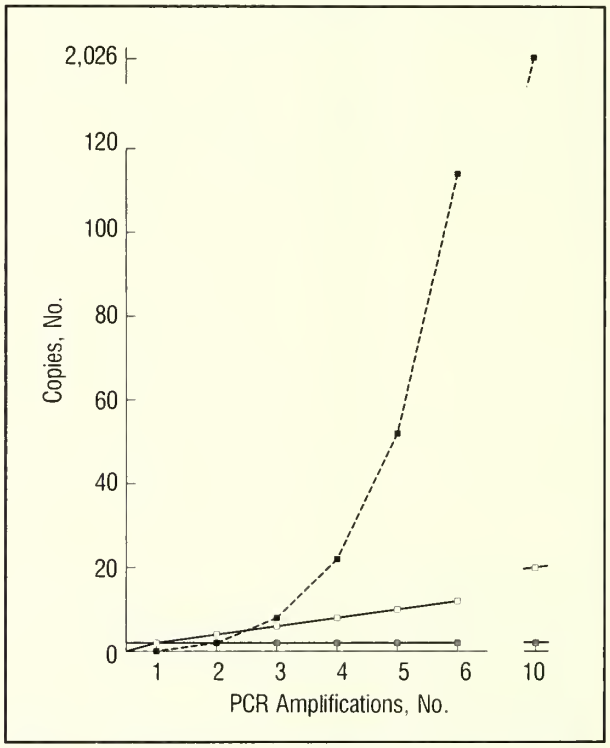

Figure 4.—The graph shows polymerase chain reaction (PCR)-amplified copies. The number of original DNA templates remains constant at 2 per haplotype, the number of longer products with a primer on one end increases linearly by 2 each cycle, and the number of unique-length sequences increases logarithmically beginning with the third amplification cycle.

This approach, or variations on it, can be used to determine the identity of alleles present in a single cell obtained by blastomere biopsy, thus leading to preimplantation diagnosis of the individual embryo.

Animal Models of Preimplantation Diagnosis

The effect of removing a portion of the early embryo on subsequent development is a major issue that had to be considered before doing preimplantation diagnosis on human embryos. Although the mouse, *Mus musculus*, is the predominant species that has been studied as a model for preimplantation embryo diagnosis, evidence from studies

of it and several domestic species indicates that there will be little, if any, lasting effect from such ablations. First, the cells of the cleavage-stage mammalian embryo (or blastomeres) appear to be developmentally equivalent and totipotent until just before the blastocyst stage.[13,14] Consequently, removing one or two blastomeres does not alter the developmental program of the early embryo, as it regulates to form a normal but smaller blastocyst. Single blastomeres of the two-cell mouse embryo (defined as one-half blastomeres) can form an intact blastocyst that develops normally to term after transfer to a foster mother with no lasting effects on an individual's size or rate of growth.[15] Although isolated one-quarter and one-eighth blastomeres of mouse embryos do not generally develop into complete blastocysts, embryos of some domestic mammals have an even greater regulatory capacity, as indicated by the development of identical siblings after the transfer of isolated one-quarter or one-eighth blastomeres to the uteri of foster mothers.[13,16] The difference between the mouse and domestic species may be the stage at which they form a blastocyst, which occurs at the 32-cell stage in mice, but at the 64-cell or later in the other species.[17] Because human embryos form a blastocyst at about the 64-cell stage,[18] they may be expected to be more similar in their regulative capacity to the domestic species than to mice. In any case, removing one or two one-eighth blastomeres from an embryo is far less a developmental challenge than forming a complete embryo from a single isolated blastomere.

Human embryos from which biopsies have been taken using the procedures described here were capable of developing to the blastocyst stage at least as frequently as unmanipulated embryos and had the same proportion of inner cell mass (destined to form the embryo proper) as trophectoderm cells (destined to form the placenta); when correction was made for the reduction in mass resulting from biopsy, they had the same number of cells at the blastocyst stage as normal embryos.[19] Therefore, biopsy procedures used in preimplantation diagnosis do not seem to substantially perturb normal embryonic development, as evidenced by successful development to term when biopsied embryos were returned to the mother by embryo transfer.[5,6]

Embryos of laboratory mammals have also been used to develop the general variables of preimplantation diagnosis. Blastomere biopsy of mouse embryos at the eight-cell stage was less detrimental to subsequent development than biopsy at earlier or later stages.[20,21] Mouse embryos biopsied at the eight-cell stage have also been cryopreserved and thawed before transfer to foster mothers, with no notable differences in the frequency of implantation or full-term development as compared with sham- and intact-control embryos.[22] Rabbit, mouse, and marmoset embryos have also been biopsied at the blastocyst stage.[23-26] Similar preclinical studies have been done with human blastocysts,[27,28] but this approach has not yet been used clinically because of the modest frequencies of human embryo development to the blastocyst stage,[18] and it is not considered further here.

Mouse embryos have been studied most extensively as a model for preimplantation diagnosis using PCR. This approach was used to diagnose homozygous embryos for the β-thalassemia,[29] the shiverer mutation in the myelin basic protein gene,[30,31] ornithine transcarbamylase deficiency or sparse fur mutation,[32] a human β-globin transgene,[33] and for sex identification on the basis of Y-specific sequences.[34-36] These studies have established PCR as an efficient and sensitive method for detecting alleles in single cells that, combined with blastomere biopsy, can be used to distinguish between normal and mutant embryos with a high degree of confidence (90% to 100%). Despite these high efficiencies of correct allele identification, continued caution is advised in transferring this approach to human embryos because of the compounding effect of errors in PCR efficiency, blastomere transfer, and inadvertent DNA contamination.[37]

In situ hybridization or other cytogenetic analyses have also been used to analyze the biopsied blastomeres of mouse embryos. In these studies 70% to 90% of embryos were successfully diagnosed with X chromosome-specific probes[38,39] or by karyotyping.[40,41] Because of the lower rates of success than with PCR and the limitation to large genetic differences that can be distinguished with these approaches, cytogenetics has not yet been used clinically for human embryos. Nonetheless, cytogenetic methods, particularly in situ hybridization, remain promising for diagnosing numerical chromosomal abnormalities in biopsied blastomeres because this cannot be done efficiently by PCR.

In sum, studies to date of animals have provided a sound preclinical basis for the continued application of preimplantation diagnosis to human embryos by PCR and will continue to serve for the development and validation of protocols for other single-gene defects by PCR and chromosomally detectable defects by cytogenetic methods.

Experience With Human Embryos

Much of the experimental analysis of human embryos has been by the use of PCR. Some initial investigations suggested the use of miniaturized enzyme systems for analyzing individual blastomeres. This approach appears not to be useful in that much of the enzyme activity in blastomeres from four- and eight-cell embryos appears to be of maternal origin. Braude and co-workers measured hypoxanthine phosphoribosyltransferase activity in individual blastomeres removed from four- to eight-cell human embryos.[42] The addition of α-amanitin to block the transcription of messenger RNA produced no change in activity. This suggests that activity at this stage is maternally inherited.

The most common analysis done on human embryos has been the determination of gender for use in the prenatal diagnosis of X-linked disorders. Handyside and associates initially reported preimplantation diagnosis from six- to eight-cell embryos in two couples at risk for X-linked adrenoleukodystrophy.[5] At the time of the report, the pregnancies were in midgestation. Recently the same

group reported on eight couples at risk for X-linked disorders.[19] Five pregnancies were achieved, two with twins and three with singleton pregnancies. Six of seven fetuses were confirmed to be female on follow-up chorionic villus sampling.

The analysis of several single-gene disorders has also been reported. The successful analysis of single human blastomeres, oocytes, or sperm has been reported for cystic fibrosis,[6,43-45] Duchenne-type muscular dystrophy,[43] and sickle cell anemia.[46,47] Handyside and colleagues reported the birth of an unaffected girl following preimplantation diagnosis for cystic fibrosis.[6]

Discussion

The successful birth of infants who have undergone preimplantation embryonic biopsy has opened a new approach to prenatal diagnosis. Many problems remain to be solved, however, before this approach can be more widely applied. The biggest problem involves the accuracy of the technique, and several issues are involved. The first is contamination of the specimen. Because PCR is being used to amplify a single cell in most cases, any extraneous DNA contamination could potentially also be amplified. Various strategies have been devised to minimize this risk, but it continues to exist. Another serious problem that is inherent to the PCR procedure is inefficient amplification. Various studies have reported amplification efficiencies using PCR with single cells of 45% to 80%.[45-48] Another amplification problem is that in as many as 29% of cases, a single allele only may amplify.[46] Several strategies to deal with these problems using coamplification have been devised.[48,49] None of these approaches completely eliminate the problem.

Another concern is the safety of the procedure to the developing embryo. As noted, "normal" infants have been born following the procedure. Too few infants have been born to know if there will be any long-term effects from this procedure, but the studies in animals argue for a minimal or insubstantial effect of biopsy on mammalian embryos in general.

This approach to prenatal diagnosis is a complicated and expensive one. The efficiency of in vitro fertilization is low, although the current statistics relate to infertile couples. The hope is that a population with normal fertility undergoing preimplantation diagnosis would have higher pregnancy rates.

Ethical issues also exist. Whereas the ethical status of the early embryo has been widely discussed, the emergence of new technologies, such as preimplantation diagnosis, raises further issues. Many people are uncomfortable with this type of early manipulation of the embryo and think that it may open the door to germ-line genetic therapy or other manipulations. Robertson feels that the selection of embryos on genetic grounds is ethically acceptable because it obviates the birth of offspring with severe genetic disorders without the need to undergo prenatal diagnosis and abortion.[50]

Clearly preimplantation diagnosis will remain an experimental procedure until these problems are solved. In addition, because of the current need for in vitro fertilization with its attendant high cost, the procedure will probably be used only by couples at high risk for having an offspring affected with a genetic disorder.

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Prenatal Diagnosis Using Fetal Cells From the Maternal Circulation

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All current methods of fetal karyotyping are invasive and carry a definite, albeit small, procedure-related risk. Because of this and testing costs, only women older than 35 years who have a greater risk for fetal aneuploidy are currently offered prenatal testing. But this detects only 20% to 25% of fetuses with Down syndrome. It would be a tremendous advance to find a noninvasive technique for prenatal diagnosis that carries no procedure-related risk and could be offered to all pregnant women. We describe a possible technique for noninvasive prenatal diagnosis that aims to identify fetal cells in the peripheral maternal circulation and successfully garner them for prenatal testing.

Early attempts at fetal karyotyping were hampered by inaccurate diagnostic methods and cumbersome cell-counting techniques. Today, improved capabilities of identifying and enriching for fetal cells, coupled with sensitive methods of analysis such as the polymerase chain reaction, bring renewed enthusiasm to this task. Many technical issues, as well as serious questions regarding the test's utility, still exist, however, and must be explored and answered before the capture of fetal cells in the maternal circulation translates into reality for noninvasive prenatal diagnosis.

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At least two reasons exist for the current increased interest in prenatal diagnosis. More women at an advanced maternal age, defined as age over 35 years at the time of delivery, are choosing pregnancy, and these women are at a considerable risk for fetal aneuploidy. In addition, because of the explosion of information in molecular genetics, an increasing number of hereditary disorders are detectable prenatally.

Currently we have three routine ways of obtaining fetal tissue: amniocentesis at 15 to 20 weeks' gestation, chorionic villus sampling at 10 to 12 weeks, and percutaneous umbilical blood sampling past 18 weeks. In addition, experimental invasive fetal sampling methods such as early amniocentesis, late transabdominal chorionic villus sampling, skin biopsy, liver biopsy, and muscle biopsy are being used. Although amniocentesis and chorionic villus sampling are both widely accepted and relatively safe, they are both invasive and carry a definite, albeit small, procedure-related risk. Because of this risk and the cost of testing, only women older than 35 who have a greater risk for fetal aneuploidy are currently offered prenatal testing. Because testing detects only 20% to 25% of fetuses with Down syndrome, finding a technique for prenatal diagnosis that is noninvasive and carries no procedure-related risk would be a tremendous advance that could be offered to all pregnant women. We describe a possible technique for noninvasive prenatal diagnosis that will identify fetal cells in the peripheral maternal circulation and successfully garner them for prenatal testing.

Distinguishing Fetal From Maternal Cells

Three major challenges must be met. First, we must distinguish fetal cells from maternal cells in a process that must be both sensitive and specific. Because the number of desired fetal cells will be small, we must have a way to select for them. By an enrichment process using techniques such as the fluorescent-activated cell sorter, various measures distinguishing fetal cells from maternal cells can be studied and used to concentrate the specimen for fetal cells. Finally, the genetic material in the collected fetal cells will be analyzed with the aid of rapid and sensitive techniques such as in situ hybridization and polymerase chain reaction.

The literature as far back as 1893 contains descriptions of the transplacental passage of fetal cells into the maternal circulation when Schmorl reported finding trophoblasts in the lungs of women dying of eclampsia.[1] Although originally thought to be due to increased uterine

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ABBREVIATIONS USED IN TEXT

FISH = fluorescence in situ hybridization
PCR = polymerase chain reaction

manipulation or maternal trauma, the transplacental passage of fetal cells during the course of normal pregnancy was later reported by many investigators. Douglas and co-workers found large cells with 30 or more nuclei and eosinophilic cytoplasm in the broad ligament veins of women with gestations as early as 18 weeks.[2] These were thought to be examples of syncytiotrophoblasts. Goodfellow and Taylor found syncytiotrophoblasts in the antecubital veins of six of ten women between 8 weeks' gestation and full term.[3] Walknowska and colleagues searched for male fetal lymphocytes by counting five small acrocentric chromosomes and labeling them "XY" cells.[4] They found such cells in 19 of 21 women who gave birth to male infants. Unfortunately, they also found such cells in six of nine women who gave birth to female infants. Schroder and de la Chapelle used quinacrine-stained portions of the Y chromosome to direct their search.[5] Although their results showed an encouraging number of positive-fluorescent cells in women pregnant with male fetuses, implying that passage of lymphocytes into maternal circulation was appreciable, the accuracy of predicting fetal sex was not appreciably better than that obtained by Walknowska's method.

All of these early investigations had a worrisome incidence of false-positive and false-negative results. False-positive results were thought to arise from artifact, nonspecific binding, or homologous areas of fluorescence on parental autosomes. False-negative results may have been due to the nondetection of the variable Y-fluorescent area because it was too small to detect or, more likely, from too few cells being counted to detect reliably the few fetal cells in the maternal circulation. A refinement of this fluorescent technique excluded mothers with bright autosomal fluorescence, which reduced the number of false-positive results, but did little for the unacceptably high percentage of false-negative results.[6]

A major improvement in the method came with the introduction of fluorescently-tagged monoclonal antibodies. A number of monoclonal antibodies raised against antigens on various fetal cells have been used. In 1984, Covone and co-workers used a murine monoclonal antibody, H315, to detect syncytiotrophoblasts in the peripheral circulation of 46 pregnant women.[7] They did not confirm the fetal origin of these cells, however, and other investigators were not able to duplicate their results. Pool and colleagues used the same antibody and did not detect H315+ cells in a quarter of 62 pregnant women tested.[8] A great variability between patients and substantial overlap between pregnant and nonpregnant women were found. Adinolfi reported that most H315+ cellular elements did not react with Y chromosome-specific probes, regardless of whether the fetus was male.[9] He postulated that maternal blood cells adsorbed H315 as they circulated through the placenta.

Mueller and co-workers screened 6,800 monoclonal antibodies to find 5 that appeared to react specifically to a membrane antigen on syncytiotrophoblasts and nonvillous cytotrophoblasts.[10] The labeled cells were then gathered using magnetic beads and proved their fetal origin by polymerase chain reaction (PCR) amplification of a Y chromosome-specific DNA sequence. Of 13 women carrying male fetuses, 12 had accurate prediction of fetal sex by this method.

A number of antigens have been studied on fetal erythrocytes. Fetal erythrocytes have been found in the maternal circulation and are thought to be the result of transplacental bleeding. The fetal circulation is distinguished from the maternal circulation because the former contains a large number of erythroid precursor cells that are nucleated and larger (200 μm^3 compared with 90 μm^3). A number of erythrocyte cell surface antigens have been examined. The first seemingly promising antigen was the transferrin receptor found on nucleated erythrocytes that were actively incorporating the iron transferrin complex. Bianchi and colleagues used a monoclonal antibody against this transferrin receptor to identify fetal erythrocytes, enriched the fetal population using cell-sorting techniques, and confirmed the presence of male (fetal) DNA in six of eight pregnancies carrying male fetuses using the PCR amplification technique.[11] The authors could detect as little as 100 pg of fetal DNA or the equivalent of 15 fetal cells. Other investigators, as well as Bianchi and associates in subsequent unpublished data, have found that the transferrin receptor has limited utility when used by itself. Ganshirt-Ahlert and co-workers used this antibody and the magnetic-activated cell sorter to enrich for nucleated erythrocytes and found that this process detected only 25% of the desired cells.[12] Others have used two surface antigens, transferrin receptor and glycophorin A, in conjunction with other physical cell measurements, size, and granularity, with all being evaluated simultaneously in a multiparameter fluorescence-activated cell sorter.[13,14] Price and colleagues sorted for fetal erythrocytes using this method, performed PCR for a single-copy Y-specific DNA sequence, and correctly identified male sex in 12 of 12 fetuses.[13] Five of six female fetuses were appropriately negative for the Y-specific DNA sequence. It appears that, although the number of fetal cells in the maternal circulation is small, with the help of a combination of specific fluorescent antibodies, cell sorting techniques, and PCR amplification, a correct diagnosis of fetal sex can be made in most cases.

Sporadic cases of aneuploidy also have been accurately detected. Price and associates detected one case of trisomy 18 in a maternal blood specimen taken one week after chorionic villus sampling and one case of trisomy 21 in a maternal blood specimen taken just before chorionic villus sampling.[13] We have seen one case of trisomy 21 in a maternal blood specimen taken two weeks after amniocentesis. A multicenter clinical trial involving thousands of women is needed to systematically study the diagnostic accuracy of fetal cells obtained from maternal blood before this test can be offered clinically.

Fluorescent-Activated Cell Sorting

Basic Principles

The flow cytometer is a sophisticated instrument for studying various physical and chemical properties of particles as they flow single file past an observation point.[15] Biologic particles of various sizes have been studied successfully, including large immune complexes, individual viral particles, liposomes, cellular organelles, bacteria, fungi, chromosomes, eukaryotic cells, cell hybrids, cell aggregates, and multicellular organisms. A number of physical and chemical characteristics can be measured. Structural features such as cell size, cell shape, DNA:RNA content, or cell surface antigens are particularly useful in distinguishing cells in a mixed population. Functional measurements such as membrane permeability, membrane integrity, enzyme activity, or surface charge are also possible. Several variables can be studied simultaneously with multiparameter cell sorters. With the aid of the computer, the characteristics of each cell are compared with preselected characteristics, and once the desired subpopulation of cells is identified, these cells are diverted to form a pool of viable cells that have been enriched for a particular cell type.

Analysis

By using cell-sorting techniques, a mixed population of fetal and maternal cells can be enriched for fetal cells. The degree of enrichment possible varies, depending on the power of the different tests used to distinguish between the fetal and maternal cell populations. Methods of analysis that require minimal amounts of DNA are helpful. For rapid and specific diagnoses using small amounts of DNA, the polymerase chain reaction method is superior. Using PCR, the amount of DNA in one or a few cells can be amplified into a quantity sufficient for prenatal detection. This is done by first denaturing or separating DNA into its two complementary strands. Oligonucleotide primers, or short starting pieces of DNA that are complementary to the desired sequence, are added in such a way that they anneal or bind to their complementary sequences. A DNA polymerase synthesizes a new strand by extending the primer sequence. By repeating these steps, many copies of the segment of DNA between the two primers are made. By using the appropriate primers, this technique can quickly establish the presence or absence of a particular sequence, such as one on the Y chromosome to determine the sex of a fetus that may be at risk for an X-linked disease. Clearly PCR can aid in the prenatal detection of diseases for which the mutation is known—sickle cell disease, cystic fibrosis, β-thalassemia—or in which the sequence at a genetically linked restriction fragment length polymorphism is known—hemophilia A.

How sensitive is the PCR technique? Theoretically it can detect the amount of DNA present in one cell. To test this sensitivity, Adinolfi and co-workers amplified DNA from one cell in cell-free media and were able to obtain a positive result.[16] The same result was obtained when the cell was placed in a background of 3,500 "undesired" cells. One cell of interest in a background of 7,000 cells gave only a weakly positive result, however. One cell among 1×10^5 background cells could not be amplified using one set of primers.

Using nested primers—one set of primers situated inside another set—Lo and colleagues were able to amplify one cell in a background of 1×10^7 negative cells and were thus able to increase the sensitivity of the PCR detection method.[17] Sensitivity was limited, however: false-positive results became a problem when the number of amplification cycles exceeded 20, illustrating the traditional problem of sacrificing specificity for increasing sensitivity.

In Situ Hybridization

Fluorescence in situ hybridization (FISH) is a useful new technique for the rapid detection of cytogenetic abnormalities. This technique uses fluorescently labeled, chromosome-specific probes to identify chromosomal aberrations, both in number and in structure. Because of its technical convenience in using nonradioactive probes and the increased availability of probes that hybridize intensely and specifically to selected chromosomes, this technique promises to have increasing use in the next few years.

Most probes bind to repeated sequences on regions of the target chromosome near the centromere. The fluorescence of the probe allows for a rapid identification of the number of copies and the gross structural makeup of the chromosomes in interphase nuclei. Lucas and co-workers used in situ hybridization to fluorescently stain regions that flank human chromosome 1p to detect structural aberrations involving this region.[18] A successful diagnosis of trisomy 18 has been reported by using amniotic fluid cells hybridized with a repetitive sequence probe that, under highly stringent conditions, is specific for the centromeric region of chromosome 18. Lichter and colleagues reported the successful rapid detection of numerical and structural aberrations of chromosome 21 in metaphase and interphase cells using DNA probes that specifically label the terminal band 21q22.3 by in situ hybridization.[19] Interphase in situ hybridization is especially promising for clinical applications where rapid results are desirable, where cells are difficult to culture in vitro, or where concern exists about the ability to stimulate a representative fraction of cells into proliferation for metaphase analysis.

In situ hybridization can be applied directly to fetal cells isolated from the maternal circulation. Specific repeat probes are currently available for chromosomes 18, X, and Y, and one probe detects both chromosomes 13 and 21. By using two different stains, such as fluorescein (yellow-green) and rhodamine (red), two different chromosomes can be visualized at the same time, thus creating a way to distinguish male fetal cells from maternal cells. Common trisomies can also be rapidly detected. Using the two-color technique, one fetal cell can be detected in 5×10^5 to 5×10^6 maternal cells.

Conclusion

The search for fetal cells in the maternal circulation has been going on for many decades. The tools for fetal cell identification and enrichment have improved considerably, and for the first time we have an extremely sensitive method of analysis in PCR. This may prove to be a crucial difference because fetal cells rarely appear in the maternal circulation. Despite these advances, several major difficulties remain.

First, the problem of false-positive and false-negative results has not been completely solved. To date, no large study has been able to predict the sex of a fetus with complete accuracy regardless of the methods of enrichment or the vehicle for analysis used. Explanations for false-positive results include PCR contamination or circulating male cells from a previous pregnancy. False-negative results could easily arise from loss of the rare fetal cells somewhere in the enrichment process. This becomes a problem in the case of FISH analysis, when scoring a cell as normal or trisomic depends on the proportion of cells counted as trisomic, not just on one cell scored as trisomic. In our experience, as many as 20% of cells can be scored as trisomic in a pure population of normal cells. Because the recovery of fetal cells is sparse at best, there may not be enough fetal cells to count to clearly distinguish a trisomic or aneuploid cell from a normal cell. Hence, although the reports of aneuploid detection from maternal blood are encouraging, they are based on aneuploidy rates as low as 2.8% of cells counted; a large series of unknown specimens should be studied to find out, in a euploid population, whether 2.8% or more of cells would also appear to have an abnormal number of dots purely from technical variability.[20]

Apart from the technical limitations revolving around the detection of a Y chromosome-specific sequence against a maternal background, numerous questions remain that pertain to the usefulness of looking at fetal cells in this manner. Certainly the test could be a noninvasive way to determine fetal sex for X-linked disorders. Beyond this, however, its usefulness may be limited. Detecting a Y chromosome sequence against a negative background of maternal cells is one thing, but detecting point mutations or even large deletions by PCR or FISH may prove impossible. In X-linked or autosomal recessive disorders, the inability to quantitate the dose of abnormal chromosomes present will be a major handicap. Against a background of cells from a woman who is a carrier and who has both normal and abnormal gene sequences, a definitive diagnosis of the fetal genotype by PCR will be difficult. In autosomal dominant disorders, again, the test will be difficult to interpret in all cases where the mother is affected and carries both normal and abnormal sequences in the background against which the fetal cell must be evaluated. Finally, to attain the wealth of information available by invasive methods today, the fetal cells after identification and separation must be viable to provide metaphase preparations for cytogenic studies.

Whether fetal cells cross the placenta into the maternal circulation and, if so, whether they do so in a sufficient number to allow for prenatal diagnosis are questions that have been debated for several decades. Early attempts to answer these questions were hampered by inaccurate diagnostic methods and cumbersome cell-counting techniques. Today we have improved capabilities for identifying fetal cells using a variety of cell surface-specific antigens and flow cytometry techniques to enrich for the fetal cell population in the maternal circulation. The DNA in the few fetal cells selected in this way can then be amplified with sensitive methods of analysis such as the polymerase chain reaction and analyzed with in situ hybridization. Many technical issues, as well as serious questions regarding the test's utility, still exist and must be explored and answered before the capture of fetal cells in the maternal circulation translates into reality for noninvasive prenatal diagnosis.

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Maternal Serum Screening for Neural Tube Defects and Fetal Chromosome Abnormalities

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Second-trimester maternal serum screening is a noninvasive means of identifying pregnant women at an increased risk for various conditions including a fetus with open spina bifida, fetal Down syndrome, trisomy 18, multiple gestation, and adverse pregnancy outcome. Combinations of several different markers are available for screening. These include α-fetoprotein, human chorionic gonadotropin, and unconjugated estriol. In this review, we discuss the benefits and limitations of the screening tests and the suggested protocols for the care of patients.

(Rose NC, Mennuti MT: Maternal serum screening for neural tube defects and fetal chromosome abnormalities, *In* Fetal Medicine [Special Issue]. West J Med 1993; 159:312-317)

Maternal serum screening is the earliest noninvasive biochemical method of obtaining information about a fetus. The object of a medical screening test is to identify among a healthy population a small group of patients that is at a sufficiently increased risk of having a fetus with a disorder to be offered a specific diagnostic test. During pregnancy, biochemical screening markers are used to select the women who may be offered ultrasound examinations, amniocentesis, or other obstetrical intervention. The use of these prenatal screening tests has expanded from identifying fetuses at risk for neural tube defects to those with fetal chromosome abnormalities, as well as women at risk for third-trimester obstetrical complications. Maternal serum screening programs have the potential to decrease fetal morbidity and mortality by providing access to earlier diagnosis, by enabling families to make more informed reproductive decisions, and by designing appropriate delivery strategies. Combinations of three different markers are measured in maternal serum screening programs: α-fetoprotein (AFP), human chorionic gonadotropin (hCG), and unconjugated estriol.

Maternal Serum α-Fetoprotein Testing

Neural Tube Defects

Maternal serum AFP, the most commonly measured maternal serum marker, is ideal for fetal evaluation because under normal conditions it is produced solely by the fetus. Both high and low AFP values may be predictive of a birth defect or adverse pregnancy outcome. The association between the AFP value and fetal abnormalities was first recognized in 1972, when Brock and Sutcliffe measured AFP levels in the amniotic fluid of 31 pregnancies with anencephaly and 6 with spina bifida, hydrocephaly, or both.[1] All of the cases of anencephaly and most of the spina bifida cases before 30 weeks' gestation were associated with amniotic fluid AFP levels that were markedly elevated. The basis for this observation is that when the fetus has an "open," or non–skin-covered defect, AFP leaks across the exposed capillaries from the fetal circulation into the amniotic fluid. The α-fetoprotein is also transferred across the amnion and the placenta into the maternal circulation. In 1974 Wald and co-workers did a case-controlled study comparing maternal serum AFP levels in 7 women carrying fetuses with open neural tube defects with 14 control women matched for maternal age, parity, and gestational age.[2] Maternal serum AFP values were significantly higher in the affected pregnancies than in the control population. This observation was validated by the United Kingdom Collaborative Study in 1977,[3] which demonstrated the usefulness of maternal serum AFP values in prospective screening tests for open neural tube defects.

Neural tube defects are the second most common serious fetal malformation in the United States, surpassed only by congenital heart defects. They are a heterogeneous group of disorders resulting from the failure of normal neural tube closure between the third and fourth week of embryologic development. The cranial end of the neural tube eventually becomes the forebrain, midbrain, and hindbrain, and a failure of closure results in acrania or anencephaly. The caudal end of the neural tube becomes the spinal cord, and a failure of closure results in spina bifida. A third type of neural tube defect, the encephalocele, is defined as cystic extensions of the brain through an overlying scalp and skin defect. Encephaloceles are much less common than spina bifida or anencephaly.

In the United States, the incidence of neural tube de-

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ABBREVIATIONS USED IN TEXT

AFP = α-fetoprotein
hCG = human chorionic gonadotropin
MoM = multiple of the median

fects is 1 to 2 per 1,000 births. Their etiologic heterogeneity was noted by Holmes and associates, who reported that of 106 live-born or stillborn infants with a neural tube defect, about 12% had identifiable causes.[4] The various causes of these defects are listed in Table 1. Most (85%) neural tube defects are due to multifactorial inheritance—that is, a genetic predisposition due to an interplay between several genes and environmental factors—but 90% to 95% occur in couples without a family history of these defects.

At the most commonly applied cutoff levels, maternal serum AFP screening detects about 85% of cases of open fetal neural tube defects, consisting of 80% of fetuses with open spina bifida and 90% of those with anencephaly. The combination of maternal AFP screening and ultrasonography will detect more than 99% of cases of anencephaly. In contrast, most encephaloceles are skin covered[5(p191)] and are therefore less likely to be detected by maternal AFP screening or amniocentesis, but are more often diagnosed by ultrasonogram. Although maternal serum AFP screening was designed to detect neural tube defects, the use of this testing has been expanded to include many other abnormalities, including ventral wall defects, congenital nephrosis, and fetal death (Table 2).

Reporting Maternal Serum α-Fetoprotein Levels

The object of a screening test is to maximize detection at an acceptable false-positive rate. These biochemical markers are typically reported as a multiple of the median (MoM). This statistical convention was introduced by the First UK Collaborative Study on maternal serum AFP as a method for participating laboratories to compare individual test results.[3] The multiple of the median is a reflection of a patient's result compared with the laboratory's median value and is not influenced by outlying values. Every laboratory ideally develops its own reference data, with a median maternal serum AFP value from unaffected pregnancies calculated for each week of gestation. For AFP, the absolute value of a pregnant woman's AFP level is modified by other factors that affect the result. These include an inverse relationship with maternal weight, higher AFP levels in African Americans than in whites, and lower levels in women with insulin-dependent diabetes mellitus. The adjusted result is expressed as a multiple of the median by dividing the maternal serum AFP concentration by the median value for that week of gestation. A log gaussian distribution of maternal serum AFP levels is shown in Figure 1. The median maternal AFP value for each week of gestation is designated as 1.0 MoM. Most screening programs establish a cutoff of 2.0 or 2.5 times the median value (2.0 to 2.5 MoM) when compared with normal controls at the same week of gestation. Each cutoff point is a balance between the detection rate and the false-positive rate: the higher the screening cutoff value, the lower the false-positive rate but the lower the detection rate. For example, at a 2.0-MoM cutoff, the false-positive rate is about 4%, whereas a 2.5 MoM cutoff has about a 2% false-positive rate. Selecting an appropriate cutoff level is also influenced by the prevalence of the disorder in the population to be screened. The most common causes of false-positive and false-negative maternal AFP results are listed in Table 3.

TABLE 1.—*Causes of Neural Tube Defects*

- Multifactorial inheritance
- Single-gene (autosomal recessive) disorders
  - Meckel's syndrome (most common)
  - Robert's syndrome
  - Jarcho-Levin syndrome
  - Median facial cleft syndrome
  - HARDE (Walker-Warburg) syndrome
  - Oculoauriculovertebral dysplasia (Goldenhar's syndrome)
- Chromosomal aneuploidy
  - Trisomy 18
  - Trisomy 13
  - Trisomy 21
  - Triploidy
  - Unbalanced translocations, markers, ring chromosomes
- Teratogenic agents
  - Valproic acid
  - Carbamazepine
  - Aminopterin
  - Thalidomide
- Amniotic band sequence
- Cloacal extrophy
- Sacrococcygeal teratoma
- Maternal insulin-dependent diabetes mellitus

HARDE = *h*ydrocephalus, *a*gyria, *r*etinal *d*ysplasia, and *e*ncephalocele

TABLE 2.—*Abnormalities Identified by α-Fetoprotein Screening*

- Ventral wall defects
  - Omphalocele
  - Gastroschisis
- Triploidy
- Trisomies 18, 13, and 21
- Unbalanced translocations
- Amniotic band sequence
- Pentalogy of Cantrell—omphalocele, lower sternal defect, deficiency of diaphragmatic pericardium, intracardiac abnormality, anterior diaphragmatic defect
- Renal agenesis
- Fetal demise
- Multiple gestation
- Congenital nephrosis (Finnish type)
- Sacrococcygeal teratoma
- Dermatologic disorders
  - Epidermolysis bullosa
  - Congenital ichthyosiform erythroderma
- Chorioangioma
- Risk of poor perinatal outcome
- Maternal hepatoma
- Maternal ovarian teratoma

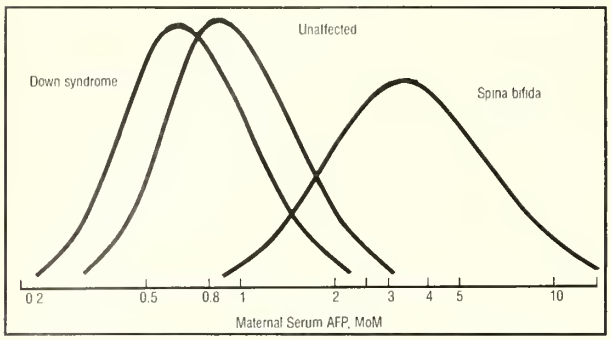

Figure 1.—The graph shows the log gaussian distribution of maternal serum α-fetoprotein (AFP) levels between 16 and 18 weeks' gestation in singleton pregnancies screened for open spina bifida, normal pregnancies, and those with fetuses with Down syndrome. MoM = multiple of the normal median

TABLE 3.—*Common Causes of False-Positive and -Negative Maternal Serum α-Fetoprotein (AFP) Levels*

False-positive levels
Inaccurate gestational dating—patient has a more advanced gestation than estimated
Multiple gestation
Race—African Americans physiologically have higher AFP levels than do whites
Low maternal weight—<41 kg (90 lb)
Spontaneous fetal-to-maternal bleeding
False-negative levels
Inaccurate gestational dating—patient has less advanced gestation than estimated
Maternal insulin-dependent diabetes mellitus
Obesity

Maternal serum AFP screening is most accurate when done between 16 and 18 weeks' gestation, but it can be done between 15 and 22 weeks. Screening earlier or later than the optimal gestational age decreases the sensitivity of the test. As with other types of screening, this test should be voluntary and should be done after counseling regarding its limitations and benefits. The patient should understand that a normal maternal AFP result does not ensure a child without an abnormality (including a neural tube defect or fetal chromosome abnormality). Conversely, an abnormal value does not diagnose an abnormality but rather indicates that the patient is at a level of risk that warrants further testing. A protocol for evaluating the pregnancies of women with an elevated maternal AFP level is shown in Figure 2.

Evaluating Elevated α-Fetoprotein Levels

Ultrasonography. Ultrasonography and amniocentesis are used to differentiate the causes of a maternal AFP elevation. Because the underestimation of gestational age is the most common reason for an elevated maternal AFP level, an ultrasonogram to verify gestational age is done first. If the gestational dating used for interpretation is inaccurate, then the multiple of the median is recalculated using the gestational age as determined by the fetal biparietal diameter. If the gestational dating is correct, then a high-resolution ultrasonogram is performed to identify structural malformations. Several investigators have suggested that ultrasonography alone is an acceptable alternative to amniocentesis for the diagnosis of a neural tube defect, particularly in those women with an AFP level in the range of 2.0 to 3.0 MoM.[6,7] The accuracy of ultrasonography in detecting spina bifida is about 90% and is limited by the location or extent of the lesion, the fetal position, quality of the images, and experience of the sonologist. Thus, a modification of this protocol should be based on these factors.

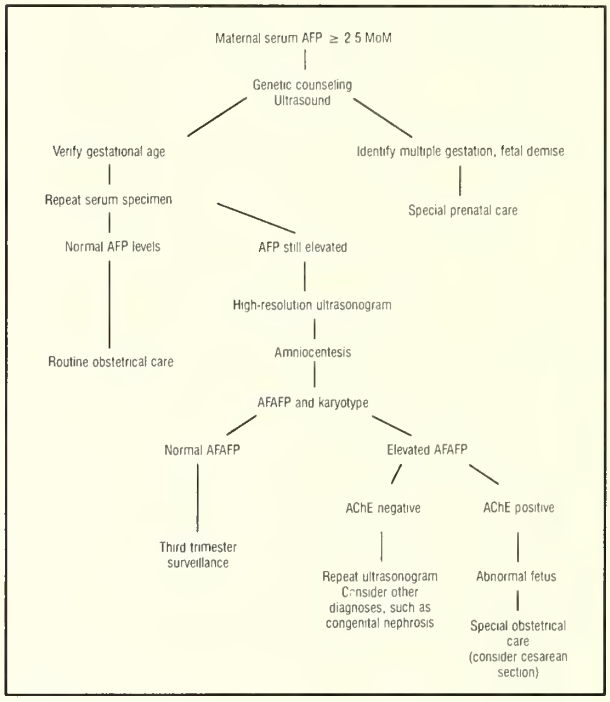

Figure 2.—The suggested protocol can be used for women with elevated maternal serum α-fetoprotein (AFP) levels. AChE = acetylcholinesterase, AFAFP = amniotic fluid α-fetoprotein, MoM = multiple of the median

Amniocentesis. Amniocentesis can be used to differentiate the cause of an elevated maternal AFP value that remains unexplained by ultrasonography. An elevated amniotic fluid AFP level suggests that the fetus has an open defect. A second test for the presence or absence of acetylcholinesterase is used to differentiate a neural tube defect from other fetal defects. Acetylcholinesterase is an enzyme contained in blood cells, muscle, and neural tissue. When the fetus has an open neural tube defect, both the AFP and acetylcholinesterase levels are usually elevated. Elevated amniotic fluid AFP without detectable acetylcholinesterase suggests an open fetal defect other than a neural tube defect. If the patient has an elevated maternal AFP value, normal amniotic fluid AFP level, and normal ultrasonogram, then an open fetal defect is excluded with a high degree of confidence. These women, however, are considered to be at an increased risk for certain obstetrical complications.[8,9] Increased fetal surveillance during the remainder of their pregnancies should be considered.

If a neural tube defect has been identified, a fetal karyotype obtained by amniocentesis and fetal echocardiography are recommended before discussing the prognosis. The morbidity and mortality of such lesions have been extensively addressed by many investigators.[10-12] If the parents elect to continue the pregnancy, serial ultrasonograms are done to detect the development of hydrocephaly and polyhydramnios.

The benefits of cesarean section delivery of infants with spina bifida have recently been reported by Luthy and colleagues.[13] In this retrospective analysis, affected infants born before labor begins had better motor function than those undergoing labor before cesarean section or vaginal delivery. Infants delivered without labor retained greater neurologic function at an average of 3.3 spinal segments above those born after labor regardless of the ultimate type of delivery. There is concern, however, regarding ascertainment bias in this retrospective review of lesions identified antenatally that may have resulted in altered obstetric management.

Preventive Therapy for Neural Tube Defects

Neural tube defects are one of the few malformations for which preventive therapy is available. A variety of temporal and demographic correlations including a higher frequency of these defects in lower socioeconomic classes have contributed to the theory that nutritional deficiencies may be a causative factor. Several studies have examined the use of vitamin supplementation (particularly folic acid) in patients with a history of a neural tube defect during pregnancy.[14-17] In a landmark study recently reported, the recurrence of neural tube defects was prevented by the administration of folic acid.[18] This prospective, randomized, controlled trial demonstrated that women who had had previous pregnancies with neural tube defects had a 72% reduction in their recurrence risk when supplemented with 4 mg per day of folic acid at least four weeks before conception and continuing through the first trimester. Preconceptional folic acid supplementation is currently recommended for preventing the recurrence of neural tube defects in these patients. Because they may recur despite vitamin supplementation, genetic counseling regarding antenatal diagnosis is still recommended for these families.

Screening for Down Syndrome

Maternal Serum α-Fetoprotein

Maternal serum AFP screening for neural tube defects had been successfully applied for about a decade before Merkatz and co-workers reported the association between low maternal AFP levels and fetal aneuploidy.[19] They noted a 25% lower level of maternal AFP in women with fetuses with Down syndrome than in unaffected pregnancies. Several prospective studies verified this association, including a multicenter collaborative study in New England that detected about 25% of cases of fetal Down syndrome (in women younger than 35) with an amniocentesis rate of 3% to 5%.[20]

The median maternal serum AFP value for a woman carrying a fetus with Down syndrome is about 0.8 MoM for normal control pregnancies (see Figure 1). The extensive overlap in the distribution of values between normal pregnancies and those affected with Down syndrome implies that selecting a cutoff level in which women are considered at a higher risk for fetal Down syndrome based on a combination of age and maternal AFP levels involves a greater level of compromise between the detection and the false-positive rate than that for open neural tube defects and the false-positive rate. Most often maternal AFP screening cutoff values are set at such a level that a woman would be considered at an increased risk when the combination of her age at the time of delivery and her AFP level indicates a risk that is equal to or greater than that of a 35-year-old woman. Thus, for women younger than 35, this approach uses a sliding scale of age-specific cutoffs, with a lower cutoff level for younger women and a higher one for older women.[21]

Human Chorionic Gonadotropin

Prenatal laboratories have used maternal serum AFP levels to screen for both fetal Down syndrome and neural tube defects concurrently. Over the past five years, other serum analytes have been reported to enhance the detection rate of fetal Down syndrome. In 1984 Chard and colleagues first suggested that serum human chorionic gonadotropin might be a useful marker in detecting fetal Down syndrome, but they did not offer any supportive clinical data.[22] This was followed by the work of Bogart and associates in which 11 of 17 women carrying fetuses with Down syndrome had hCG levels at 2.5 MoMs or greater[23]; this observation was confirmed by others.[24] Because the median hCG level in affected pregnancies is so elevated in relation to normal controls, hCG is the most effective biochemical marker in Down syndrome screening. In fact, other placental products such as human placental lactogen, progesterone, and the free β-subunit of hCG all have higher levels in Down syndrome pregnancies, suggesting that a hypersecretory or immature placenta may be the source of these abnormalities.

Maternal Serum Unconjugated Estriol

In 1988 Canick and co-workers demonstrated lower second-trimester levels of maternal serum unconjugated estriol in women carrying fetuses with Down syndrome, with a multiple of the median value of 0.79.[25] The synthesis of unconjugated estriol, a steroid hormone, is modulated by the placenta, fetal adrenal glands, and fetal liver. Like AFP, the synthesis of unconjugated estriol is about 25% lower in affected pregnancies.

Screening Using All Three Markers

In 1988 Wald and associates compared the serum findings of 77 women carrying fetuses with Down syndrome with 385 matched controls.[26] Gaussian distributions for all three analytes were established. Using a statistical method to combine these distributions with maternal age, individual risks were generated for women

of all ages. Using a risk for fetal Down syndrome of 1:250 (the risk of a 37-year-old woman at term), they identified 67% of cases of fetal Down syndrome. The risk cutoff of a 37-year-old woman was used to maintain the false-positive rate (or amniocentesis rate) at about 5%. This detection rate is significantly better than the detection rate of 20% to 25% with maternal serum AFP alone. Recently three groups have verified this finding prospectively.[27-29] Philips and co-workers evaluated 9,530 women younger than 35 years with these biochemical markers and found 7.2% to initially have a positive test—that is, a risk greater than or equal to that of a 35-year-old woman.[27] After an ultrasound examination to verify gestational age, 4.0% remained positive; 57% of cases of fetal Down syndrome were detected, with a 3.2% false-positive rate. Haddow and associates prospectively screened 25,507 women of all ages (including those older than 35).[28] Again using a term screening cutoff of 1:250, 6.6% of patients were initially positive. Of these patients, only 3.8% remained in the high-risk category after ultrasonogram evaluation, and 58% of cases of fetal Down syndrome were detected. Cheng and colleagues screened 7,718 women of all ages, identifying 6% as positive after an ultrasound examination.[29] In this report, 20 of 22 cases of fetal Down syndrome were identified, yielding a sensitivity of 91% and a specificity of 94%. Therefore, 1 case of fetal Down syndrome was detected for every 23 women offered amniocentesis, and 1 was found for every 17 amniocenteses done. In contrast, if all women of advanced maternal age underwent amniocentesis, 1 case of fetal Down syndrome would be detected for every 140 amniocenteses.

As shown by these prospective series, screening using these three markers is exquisitely sensitive to inaccuracies in gestational dating. If the gestational age is overestimated, then the initial screening test is likely to be positive. For example, consider a woman who is at 16 weeks' gestation, but is recorded as 18 weeks because of poor dating criteria. Because both AFP and unconjugated estriol levels increase during the second trimester and hCG levels decrease during this period, her AFP and unconjugated estriol values will appear low and her hCG value will appear high, a profile consistent with fetal Down syndrome. A two-week discrepancy in gestational dating can change a calculated Down syndrome risk tenfold. To lower the false-positive rate, a woman should have ultrasonographic confirmation of gestational dating by a crown-rump length or biparietal diameter before her test result is interpreted. It is important that femoral lengths or composite gestational dating (biparietal diameter plus femoral length) not be used to determine gestational age because Down syndrome fetuses have shortened long bones on second-trimester ultrasonograms.[30] Depending on the laboratory's protocol, gestational dating is changed when there is a discrepancy between the date of the last menstrual period and ultrasonographic findings of 10 to 14 days.

Currently there are no data to apply this test to multiple gestations or women with insulin-dependent diabetes. There are only limited data for applying correction factors for weight and race to hCG and unconjugated estriol, although laboratories routinely apply them to the AFP component of the test. A sample protocol is shown in Figure 3.

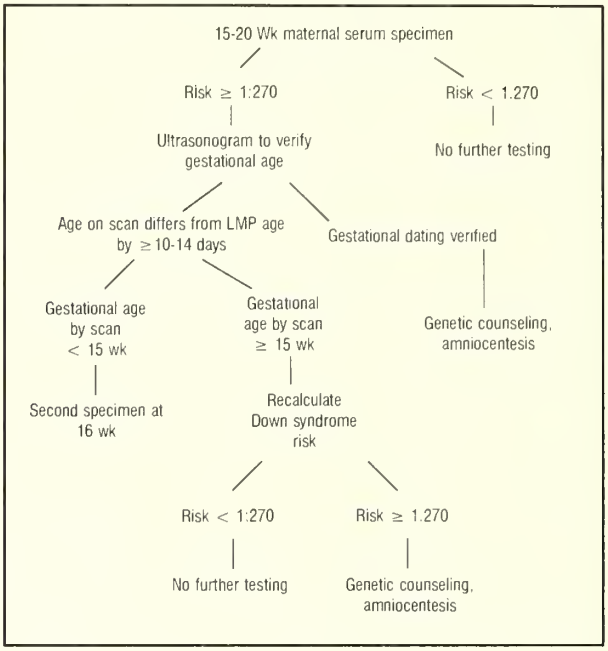

Figure 3.—A screening protocol using all 3 markers is shown. LMP = last menstrual period

Another advantage of screening with all three markers is the ability to detect trisomy 18. In contrast to the biochemical profile in fetal Down syndrome in which the AFP and unconjugated estriol levels appear low and the hCG values appear elevated, all three markers in trisomy 18 are substantially lower than expected. Therefore, the trisomy 18 risk can be calculated using the same laboratory tests. Using fixed MoM cutoff levels for ten affected patients with an AFP level of 0.75 MoM or less, an unconjugated estriol level of 0.6 MoM or less, and an hCG level of 0.55 MoM or less. Canick and co-workers identified 60% of pregnancies with trisomy 18 that were retrospectively identified with an amniocentesis rate of 0.4%.[31]

Some screening programs omit unconjugated estriol from their protocol and use hCG and AFP testing alone. Clearly, hCG is the most powerful marker for the detection of fetal Down syndrome. Although it only marginally increases the detection rate, there are two advantages of incorporating unconjugated estriol into a screening protocol. This analyte has been shown to decrease the positive rate by about 25%, decreasing the need for amniocentesis and amniocentesis-related losses and costs while maintaining the 60% detection rate. In addition, it is an important component of the trisomy 18 testing protocol. In effect, patients who undergo serum testing for AFP, hCG, and unconjugated estriol levels are screened for three specific disorders: Down syndrome, trisomy 18, and neural tube defects (and other open fetal defects). The incidence of both Down syndrome and trisomy 18 increases with

advancing maternal age,[32] whereas neural tube defects occur on a multifactorial basis.

Maternal Serum Screening for Women Aged 35 and Older

Because women aged 35 or older have a higher empiric risk for fetal aneuploidy, they are routinely offered invasive diagnostic testing for prenatal diagnosis. Because fetal loss is not associated with maternal serum screening, some patients at or older than 35 may consider having a revised estimate of their risk through triple-marker screening before deciding whether to undergo amniocentesis. About 20% of all fetuses with Down syndrome occur in older women; most occur in women younger than 35 years, for whom multiple-marker screening tests are traditionally done. Maternal age plays a pivotal role in formulating the risk for Down syndrome because the risk calculation is heavily weighted by advancing maternal age. Therefore, both the detection rate for fetal Down syndrome in older pregnant women and the amniocentesis (or false-positive) rate will increase sharply in this older age group.[28,29] Although biochemical screening in older women may more accurately determine the risk of fetal Down syndrome than screening the younger age population, it must be stressed to the obstetric patient that this screening test will not detect all cases of fetal Down syndrome and that current standards of obstetric care mandate offering prenatal diagnosis to older women.

Another important limitation of maternal serum screening in the older population is that it does not detect all chromosomal aneuploidies that are increasingly likely to occur with advancing maternal age. Specifically, several sex chromosome anomalies (such as 47,XXY and 47,XXX) would be detected by a prenatal diagnostic procedure, but are not detected by maternal serum screening. The finding of a sex chromosome abnormality raises extremely difficult counseling issues. This is shown by two retrospective series in which 38% and 62% of women informed that they carried a fetus with a sex chromosome aneuploidy elected to terminate the pregnancy.[33,34]

Conclusion

Thus, patients need to understand the benefits and limitations of maternal serum screening before they consent to this voluntary test. Although this protocol does not increase the risk of pregnancy loss in the way invasive diagnostic procedures such as amniocentesis or chorionic villus sampling do, it also does not detect all cases of fetal aneuploidy and does not specifically detect sex chromosome aneuploidies. Biochemical screening, however, has the benefit of a more precise risk assessment for fetal Down syndrome without the risk of fetal loss attributable to invasive prenatal diagnosis.

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Intrauterine Transfusion With Red Cells and Platelets

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Having direct access to the fetoplacental circulation by ultrasound-directed needle puncture has led to therapeutic interventions for fetal anemia and thrombocytopenia. Most cases of red cell alloimmunization associated with fetal anemia are caused by the antibody to the D red cell antigen. The intravascular transfusion of red cells to a hydropic fetus in such cases has notably improved survival. Nonimmune hydrops fetalis due to maternal parvovirus infection has also been treated successfully with the intravascular transfusion of red cells, whereas fetomaternal hemorrhage has not proved amenable to such therapy. Sensitization to the PLA-1 platelet antigen is the most common cause of fetal thrombocytopenia in maternal platelet alloimmunization. Fetal platelet transfusions have not proved to be a practical therapeutic modality for this disorder owing to the short half-life of the platelets. Platelet transfusions to the fetus just before delivery may avert the need for cesarean section in cases of severe thrombocytopenia.

(Moise KJ Jr: Intrauterine transfusion with red cells and platelets, *In* Fetal Medicine [Special Issue]. West J Med 1993; 159:318-324)

Twenty years ago, the fetus was merely a passenger in a concealed environment that could be pierced only by radiographic studies. With the development of real-time ultrasonography, the fetus was elevated to the status of a patient. Despite improvements in imaging technology in the late 1970s, the fetal hematologic status could be assessed only indirectly through the measurement of bilirubin levels in the amniotic fluid.[1] In 1973 Valenti described the use of a 27-gauge needle introduced through an 18-F "laparoamnioscope" to puncture the chorionic plate blood vessels under direct visualization.[2] This procedure came to be known as fetoscopy.[3] Unfortunately, a fetal mortality rate of 5% complicated the procedure, severely restricting the number of applications.

In 1983 Daffos and co-workers described the exciting new technique of percutaneous umbilical blood sampling, whereby a 20-gauge needle was directed into the umbilical vessels under real-time ultrasonographic guidance.[4] The technique gained widespread acceptance with an acceptable fetal loss rate of approximately 1%.[5] The number of applications increased until as many as 23 have been described recently.[6] As more pregnant women underwent diagnostic procedures, the likelihood of finding a series of unaffected fetuses increased. Normal hematologic values for gestational age were thereby established, and the field of fetal hematology was born. The fetal hematocrit and leukocyte count increase with advancing gestational age, and erythroblast and reticulocyte counts decline.[7-9] The fetal platelet count remains fairly stable throughout gestation.[7]

The direct treatment of fetal anemia in such disorders as red cell alloimmunization, fetomaternal hemorrhage, and parvovirus infection has become possible. Therapy for fetal thrombocytopenia due to platelet alloimmunization has also been undertaken.

Intrauterine Transfusion of Red Cells

Red Cell Alloimmunization

Etiology. Although the human maternal and fetal circulatory systems are anatomically separate, flow cytometry studies have shown that small fetomaternal hemorrhages occur in virtually all pregnancies.[10] When fetal erythrocytes containing red cell antigens foreign to the mother gain access to the maternal circulation, antibodies form in a condition known as red cell alloimmunization. Because the placenta actively transports immunoglobulin (Ig) G antibodies into the fetal circulation, antibody-antigen interactions occur on the fetal red cells. Although most of these antibodies do not fix complement, cell-mediated destruction of antibody-opsonized erythrocytes is thought to take place in the fetal spleen, resulting in fetal anemia. Although the Rh or D antigen is the most common cause of red cell alloimmunization, more than 43 other red cell antigens have been implicated in hemolytic disease of the newborn.[11] Antibodies to c, Kell, Duffy (Fy^a), and Kidd (Jk^a and Jk^b) antigens constitute the

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ABBREVIATIONS USED IN TEXT

CMV = cytomegalovirus
Ig = immunoglobulin

other major causes of red cell alloimmunization in pregnancy.

Incidence. Before the use of Rh immune globulin, 0.5% to 1.0% of all pregnant women were Rh-immunized.[12] Current recommendations for the routine administration of Rh immune globulin at 28 weeks' gestation and following delivery have dramatically reduced the incidence of Rh alloimmunization.[13] Data from the Centers for Disease Control noted that the incidence of Rh hemolytic disease of the newborn in the United States in 1984 was 10.6 cases per 10,000 total births.[14] Solola and associates reviewed seven previous series of Rh-positive pregnant women screened for irregular red cell antibodies.[15] In all, 400 cases of irregular antibodies were noted in the 131,898 patients, for an overall incidence of 1:330. Of the 400 infants in the series, 30 required exchange transfusions for hemolytic disease of the newborn. In their own population, Caine and Mueller-Heubach found 127 cases of Kell alloimmunization in 127,076 pregnancies (0.1%), 13 of which resulted in an affected fetus or newborn.[16] Two intrauterine deaths and one neonatal death occurred.

Diagnosis. Figure 1 depicts a typical plan of management for a pregnant woman with red cell alloimmunization.[17] An indirect Coombs' test should be performed in all women at their first prenatal visit. If an antibody is identified that has been associated with hemolytic disease of the fetus or newborn, a titer should be obtained. Paternal blood type and genotype should be determined. If the paternal blood type does not match the involved red cell antigen, the fetus will be unaffected, and further testing is unwarranted if paternity is certain. In cases of a paternal blood type that matches the involved red cell antigen or when the paternal status is unknown, maternal titers should be repeated at monthly intervals until a titer is obtained that indicates the fetus is at serious risk for the development of hydrops fetalis. If a heterozygous paternal genotype for the involved antigen is noted, percutaneous umbilical blood sampling can be offered to determine the fetal blood type. In half of such cases, the specific antigen will be absent from the fetal red cells and the fetus will be unaffected. Care should be taken to avoid puncturing the placenta with the sampling needle because a disruption of chorionic villi with leakage of fetal cells into the maternal circulation may increase the maternal antibody level, with subsequent worsening of the fetal anemia.[18,19]

In cases of a homozygous paternal genotype or when the fetus is found at the initial umbilical blood sampling to have the red cell antigen, serial samplings to determine the fetal hematocrit or serial amniocentesis to determine the Δ-OD450 values can be undertaken. Amniocentesis should be repeated every ten days to two weeks until a Δ-OD450 value at the 80th percentile of zone 2 of the Liley curve is noted. Intrauterine transfusion is then undertaken. Because analysis of amniotic fluid Δ-OD450

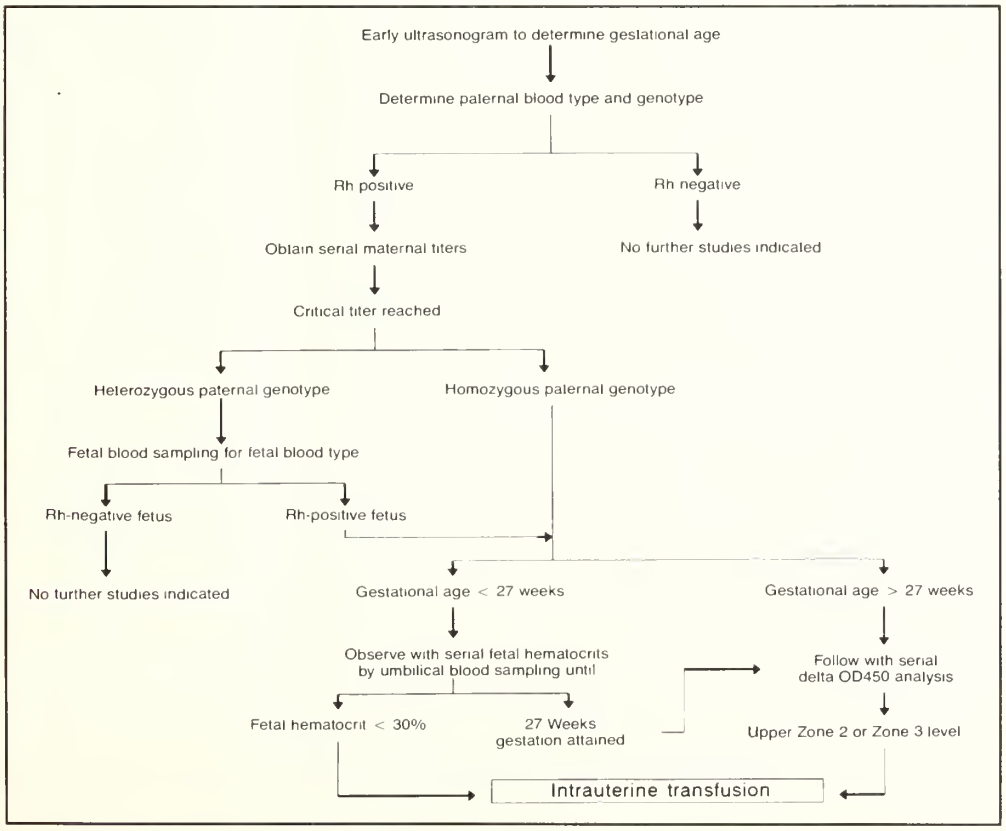

Figure 1.—The schematic shows the evaluation and treatment of red cell alloimmunization (modified from Moise et al[17]).

TABLE 1.—*University of Iowa Management Scheme for Red Cell Alloimmunization**

Hematocrit	*Reticulocyte Count*	*Direct Coombs' Test*	*Interval for PUBS, wk*	*Interval for Ultrasonogram, wk*	*Comments*
Normal	Normal	Negative to trace	--	4	If initial titer <128, repeat titer in 4 wk; if titer doubles, repeat PUBS
Normal	Normal or decreased	1+-2+	5-6	2	Do not repeat PUBS after 32 wk; deliver at term
Normal	Elevated	3+-4+	2	1	Repeat PUBS through 34 wk if stable; deliver after pulmonary maturity
Abnormal†	Any	Any	1-2	1	Repeat PUBS if hematocrit remains >0.30; deliver after pulmonary maturity
<0.30	Any	Any	--	--	Intrauterine transfusion

PUBS = percutaneous umbilical blood sampling

*Modified from Weiner et al.[21]
†A hematocrit that is >2 standard deviations below the mean value but above 0.30.

values has been found inaccurate using "modified" Liley curves before 28 weeks' gestation, serial umbilical blood sampling is the preferred method to assess fetal status if invasive testing is indicated at this point in gestation.[20] Weiner and co-workers have published guidelines regarding the frequency of serial samplings based on the initial values obtained for fetal hematocrit, direct Coombs' test, and reticulocyte count.[21] When a fetal hematocrit of less than 0.30 (30%) is noted, intrauterine transfusion is undertaken (Table 1).[21]

Technique. The first successful treatment of hemolytic disease of the fetus was described by Liley in 1963 when he introduced the technique of intraperitoneal transfusion.[22] No further modifications in technique occurred until 1981, when Rodeck and associates described the intravascular transfusion of a fetus by directing a needle into chorionic plate vessels under visualization through a fetoscope.[23] The following year, a group in Denmark reported the intravascular transfusion of a fetus by umbilical venous puncture under ultrasonographic guidance.[24]

By 1986, two schools of thought had emerged regarding the optimal method for intravascular transfusion. Investigators at Yale proposed an exchange intravascular technique similar to that used to treat hemolytic disease of the newborn in neonates.[25] Researchers at Mount Sinai School of Medicine of the City University of New York advocated a direct transfusion technique similar to that used by the Danish investigators.[26] As more experience was gained with the two techniques, the direct intravascular transfusion became more widely adopted by many centers because of its shorter procedure time. After the introduction of the intravascular transfusion, the intraperitoneal technique was virtually abandoned. The intravascular approach appeared to be a major technical advancement. An actual measure of fetal disease, the hematocrit, could be determined. In addition, red blood cells could be administered directly into the fetal circulation. In a comparative study between fetuses treated intravascularly and matched historical controls treated intraperitoneally, Harman and associates demonstrated a notable improvement in the survival of hydropic fetuses treated with the intravascular technique.[27] Survival in nonhydropic fetuses was not clearly improved by the procedure.

Despite its advantages, complications such as umbilical cord hematoma, fetal bradycardia, and porencephalic cysts not previously described in fetuses treated with intraperitoneal transfusions have been reported after intravascular therapy.[28-30] In addition, analysis of serial hematocrits from fetuses transfused with intravascular techniques reveals wide swings between transfusions. We evaluated a combined intraperitoneal-intravascular transfusion method and found it to result in a more stable hematocrit between procedures than either the exchange or direct intravascular transfusion.[31] A combined technique also allows for longer intervals between transfusions. Our technique involves administering enough packed red cells to achieve a final fetal hematocrit of 0.35 to 0.40. An intraperitoneal transfusion is then done (volume of blood to be transfused [ml] = [gestational age in weeks − 20] × 10). An intravenous dose of vecuronium (0.1 mg per kg of ultrasonogram-estimated fetal weight) is given at the start of the intravascular transfusion. This eliminates fetal movement for as long as two hours during the procedure, thereby preventing fetal injury. Transfusions are undertaken at two-week intervals for the first two transfusions, then the interval is lengthened to three to four weeks.

The end point of intrauterine transfusion is subject to debate among fetal therapists. Most centers use a target hematocrit to decide when a transfusion is complete. Advocates of direct intravascular therapy usually give transfusions to a final fetal hematocrit of 0.50 to 0.65, whereas advocates of the combined transfusion technique use 0.35 to 0.40 as a final value. Hydropic or severely anemic fetuses that are detected early in the second trimester do not tolerate intravascular transfusions as well as do older or less severely affected fetuses. A posttransfusion increase in fetal hematocrit by more than four times and an increase in the umbilical venous pressure of greater than 10 mm of mercury have both been associated with a pronounced increase in mortality in this subgroup.[32,33] For this reason, we administer transfusions to these fetuses to a final fetal hematocrit of 0.20 to 0.25 at the first treatment. A second transfusion is then done 48 hours later to achieve a final hematocrit of 0.35.

When to deliver a fetus undergoing intrauterine trans-

fusions is also a topic of considerable debate. When intraperitoneal transfusions were the sole means of in utero therapy, fetuses were routinely delivered at 32 weeks' gestation. Hyaline membrane disease and the need for neonatal exchange transfusions for the treatment of hyperbilirubinemia were common. As experience with intravascular transfusions became more widespread, fetuses were delivered at later gestational ages. Most physicians will now give the final transfusion at 35 weeks with delivery anticipated at 37 to 38 weeks. A recent (1992) cost analysis at our institution revealed that physician and hospital charges for the care of an Rh-positive fetus undergoing six intrauterine transfusions, an 11-day nursery course with 4 days of phototherapy, and readmission at 1 month of age for a final transfusion totaled more than $57,000.

In the past, O-negative, cytomegalovirus (CMV)-negative, heterologous red blood cells were used as the primary source of blood for intrauterine transfusion. Patient concern regarding the transmission of the human immunodeficiency virus has led several centers to use maternal blood for intrauterine transfusion. Advantages include the availability of fresh blood and the decreased chance for sensitization to new red cell antigens if some of the transfused blood escapes back into the maternal circulation. With folate and iron supplementation, these patients are easily able to maintain an adequate level of hemoglobin.[34]

Donor blood should be routinely screened for various infectious agents. The red cells are washed to remove the offending antibody and tightly packed to achieve a final hematocrit of 0.75 to 0.85. The unit is then filtered through a leukocyte-poor filter and irradiated with 25 Gy (2,500 rad) of external-beam radiation to prevent graft-versus-host reaction. Even if the pregnant woman has antibody to CMV, the blood may still be used because the dormant CMV virus is removed with the leukocytes in the filtering process. On some occasions an ABO incompatibility may be detected between a woman and her fetus after the initial umbilical blood sampling. In these cases, maternal blood should not be used due to the risk of sensitizing the fetus.

Outcome. Before the introduction of fetal or neonatal treatment, the perinatal mortality from hemolytic disease of the newborn was 40% to 50%.[35] The development in 1945 of the neonatal exchange transfusion was accompanied by a 50% reduction in perinatal mortality. Despite this innovative neonatal therapy, hydropic fetuses continued to die in utero. The introduction of the intraperitoneal fetal transfusion resulted in 50% survival of hydropic fetuses and 78% survival of nonhydropic fetuses.[35]

A survival rate after intravascular transfusion of as high as 96% has been reported by at least one center.[36] A more realistic statistic can be gleaned from a survey of 1,087 intravascular transfusions (389 fetuses) performed at 16 centers in the United States and Canada.[5] The survival rate for nonhydropic fetuses was 90% and of hydropic fetuses was 82%. Although previous studies regarding the developmental outcome of infants who had undergone intraperitoneal transfusions for severe anemia have shown no major deficits, long-term follow-up studies of infants after intravascular transfusions have not been reported to date.

Fetomaternal Hemorrhage

Substantial fetomaternal hemorrhage is the cause of fetal mortality in 1 of 1,000 births and of fetal morbidity in 1 of 800 deliveries.[37] The use of intrauterine transfusion to treat this problem has been described in five cases.[38-41] In four of these, the patient presented with a chief complaint of decreased fetal movement, and subsequent fetal monitoring revealed a sinusoidal heart rate pattern. In the fifth case, hydrops fetalis was noted as an incidental finding at the time of a routine ultrasonogram.[38] The results of a maternal Kleihauer-Betke stain were positive in all cases. A single intrauterine transfusion was done in three cases, and two were done in the remaining two. Despite this therapy, pregnancy was prolonged in only one case. In this case, an intraperitoneal transfusion at 21 weeks was successful in reversing hydrops fetalis with delivery of a normal infant at 38⅐ weeks' gestation.[38] In the other reported cases, fetal bradycardia or the return of decreased fetal movement necessitated delivery by cesarean section. Samplings in three of these fetuses revealed a falling hematocrit caused by continued fetomaternal hemorrhage. Thus, the use of intrauterine transfusion as a beneficial therapy in the treatment of fetomaternal hemorrhage should be questioned.

Parvovirus Infection

Human parvovirus B19 is the etiologic agent of fifth disease (erythema infectiosum, or "slapped cheek disease") in children. During outbreaks, household contacts or school teachers can be exposed. Approximately 50% of persons lack immunity, and 20% of these will become infected after exposure.[42,43] Although the infected pregnant woman will manifest a typical exanthema in about two thirds of cases, the remaining third will be asymptomatic.[44] Reported rates of fetal infection range from 2.5% to 38%.[45,46] Parvovirus inhibits fetal erythropoiesis with the subsequent development of aplastic anemia, nonimmune hydrops, and fetal death.

Maternal infection is usually confirmed by the finding of a specific IgM antibody that appears three to four days after the onset of clinical disease and persists for three to four months.[47] Fetal infection is thought to occur during a window of four to six weeks after maternal infection. Weekly ultrasonograms to evaluate the presence of hydrops fetalis should be done for this period. When hydrops is noted, donor red cells should be readied and percutaneous umbilical blood sampling performed. Studies of fetal blood typically show a negative direct Coombs' test, anemia, an inappropriately low reticulocyte count, normal serum bilirubin levels, elevated levels of total IgM, and elevated levels of hepatic enzymes.[48] Viral particles can be seen with electron microscopy in fetal ascitic fluid or blood.[49] In addition, viral DNA can be identified from fluids of fetal origin using specific probes.[47]

A total of eight fetuses have undergone treatment for

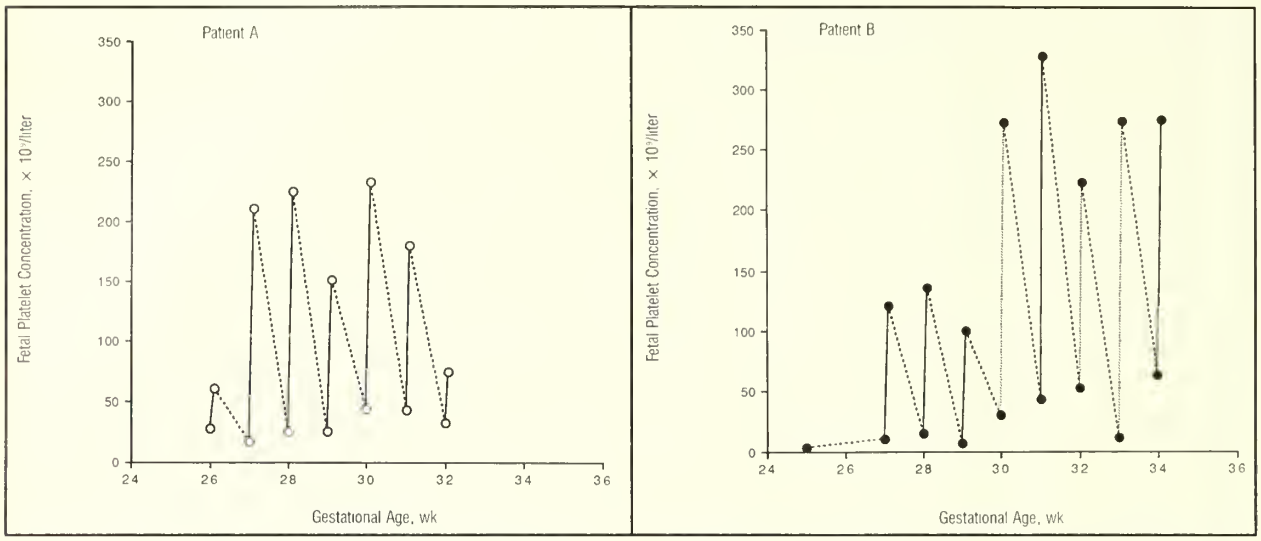

Figure 2.—Platelet counts are shown in fetuses affected by PLA-1 alloimmunization and being treated with serial intrauterine transfusions of maternal platelets: **Patient A,** 7 intrauterine transfusions were given between 26 and 32 weeks' gestation; **patient B,** 8 transfusions were given between 27 and 34 weeks' gestation. (Reprinted with permission from Nicolini et al.[61])

confirmed parvovirus infection.[44,48,50,51] All presented with hydrops and underwent intravascular transfusion. Five fetuses were transfused once, two fetuses twice, and one fetus three times. As is the case in a fetus with immune hydrops, severe fetal anemia should be corrected with serial transfusions at short intervals (one to seven days). An increase in the fetal reticulocyte count signals a recovery of the fetal bone marrow and eliminates the need for further transfusions. Experience with anemic Rh-positive fetuses undergoing intrauterine transfusions indicates that further transfusions may suppress fetal erythropoiesis and lead to fetal dependence on serial procedures to maintain the hematocrit. Nonimmune hydrops due to parvovirus infection may require several weeks to resolve after the fetal hematocrit has returned to normal. Follow-up of infants transfused for parvovirus infection has revealed normal neonatal outcomes. Based on these limited data, intravascular transfusion should be strongly considered as a therapeutic option in cases of fetal parvovirus infection and hydrops fetalis.

Intrauterine Transfusion of Platelets

Platelet Alloimmunization

Neonatal alloimmune thrombocytopenia, a disease process analogous to red cell alloimmunization, complicates 1 in 1,000 to 2,000 live births.[52] In this situation, the transplacental transfer of maternal antibodies to fetal platelet antigens of paternal origin results in severe fetal and neonatal thrombocytopenia. In utero intracranial hemorrhage occurs in 10% of cases and has been documented as early as the second trimester.[53,54] In about 75% of cases, the platelet antigen involved is the PLA-1 antigen (now called the HPA-1 antigen).[55] Unlike Rh alloimmunization, the first fetus may be severely affected, and maternal antibody titers are not predictive of the degree of fetal thrombocytopenia.[53,56] The clinician becomes aware of the disease only after an affected infant is born to the patient or her sister. Subsequent pregnancies are usually complicated by worsening fetal disease.[57]

The initial evaluation in the case of an affected neonate should include platelet antigen testing of the newborn, mother, and father. In a subsequent pregnancy, an initial cordocentesis at 20 weeks' gestation has been proposed to determine the fetal platelet count and antigen status. This approach is not without risk; 14 cases of fetal death caused by hemorrhage have occurred after fetal blood sampling in this disorder.[6] Maternal platelets for transfusion should be available at the time of the procedure in cases of excessive streaming of blood from the puncture site. Alternatively, if a rapid assessment of the platelet count can be done before the needle is removed, platelets should be infused in cases of a fetal platelet count of less than 50×10^9 per liter (50×10^3 per μl). Several authorities have proposed this threshold based on neonatal courses complicated by bleeding in infants born to women with autoimmune thrombocytopenia.[58] Because approximately 98% of the population has the PLA-1 platelet antigen, maternal platelets are usually used for fetal transfusion.[59] The platelets are obtained by apheresis 24 hours before their anticipated use, washed to remove any trace of plasma with its offending antibody, and resuspended in ABO-compatible plasma.

The volume of platelet concentrate to be used can be calculated by the formula $V = VSF\,(C_3 - C_1)/C_2$, where V represents the volume of platelets to be infused, VSF is the estimated fetoplacental blood volume for the appropriate gestational age,[8] C_1 is the fetal platelet concentration before transfusion, C_2 is the concentration of the donor platelets, and C_3 is the fetal platelet concentration desired after transfusion.[60] The optimal posttransfusion platelet count to prevent bleeding complications has yet to be determined. For this reason, most physicians will empirically transfuse a quantity of platelets based on the formula described here. Although a final fetal platelet

count should be recorded at the conclusion of the procedure, it is not necessary to await this result before removing the needle.

The first description of fetal platelet transfusions in cases of platelet alloimmunization involved serial infusions of maternal platelets by cordocentesis. Four cases have been reported to date.[60-62] In two of these, the median decline in platelets per day was 23.6×10^9 per liter. Limited experience with this technique has shown that the short half-life (four to seven days) of the platelet requires weekly transfusions to maintain an adequate fetal platelet count (Figure 2).[61] Bussel and associates have argued that this approach is associated with undue fetal risk from multiple umbilical cord punctures.[63] In an alternative approach, Lynch and colleagues successfully combined the maternal administration of steroids and weekly intravenous pooled γ-globulin to increase the fetal platelet count at delivery to greater than 50×10^9 per liter in 11 of 18 cases.[64] More important, no case of intracranial hemorrhage occurred in the treatment group, compared with a 33% incidence in antecedent siblings.[64] Therefore, serial in utero platelet transfusions are not a reasonable primary approach to the management of affected fetuses with alloimmune thrombocytopenia.

An approach proposed by Daffos and co-workers is to do a cordocentesis at term in fetuses suspected of having thrombocytopenia due to maternal platelet alloimmunization.[60] The documentation of fetal lung maturity by amniotic fluid studies obtained by amniocentesis may be indicated in women with uncertain menstrual dating. If a fetal thrombocytopenia is detected, a transfusion with previously processed maternal platelets can then be undertaken. Inducing labor with vaginal delivery would then be a safe alternative to elective cesarean section for delivery of the fetus.

Fetal transfusion of platelets just before delivery has been reported in ten cases.[56,60,62,65] Early in their experience, investigators performed the fetal platelet transfusion and then proceeded with elective cesarean section, with the reasoning that delivery by cesarean section has not proved totally protective against intracranial hemorrhage in fetuses with alloimmune thrombocytopenia.[66] Later in the series, vaginal delivery was allowed after transfusion in four of the ten cases without evidence of adverse neonatal sequelae. Sia and associates suggested that this approach was permissible only when the posttransfusion fetal platelet count was greater than 100×10^9 per liter.[66] The intrauterine transfusion of maternal platelets in fetuses found to be thrombocytopenic ($<100 \times 10^9$ per liter) at percutaneous umbilical blood sampling just before delivery deserves further study before it gains widespread acceptance.

Other Indications

Pronounced fetal thrombocytopenia has been associated with severe hydrops fetalis caused by red cell alloimmunization or parvovirus infection.[48,67] In these cases, random-donor platelets should be available at the time of the intrauterine transfusion of red cells. If a fetal platelet count of less than 50×10^9 per liter is noted in the pretransfusion specimen, the administration of an appropriate volume of platelets may prevent fetal death due to prolonged bleeding from the umbilical vessel puncture site.

Conclusion

The intrauterine transfusion of red cells in cases of fetal anemia due to red cell alloimmunization or parvovirus infection has improved fetal survival substantially. Fetal platelet transfusions in cases of platelet alloimmunization appear to have a limited therapeutic role because of the short half-life of this blood component.

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Fetal Drug Therapy

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Fetal drug therapy encompasses several areas, including the prevention of external genital masculinization in 21-hydroxylase deficiency syndrome (congenital adrenal hyperplasia), biochemical amelioration of methylmalonic acidemia, and biotin-responsive multiple carboxylase deficiency. The correction of cardiac arrhythmias has become relatively commonplace, and a reduction in the risks of neural tube defects is now possible with the use of preconceptual and early conceptual folic acid. Similarly, fetal function can be altered by the induction of fetal lung maturity using a number of agents; corticosteroids are the most common fetal pharmaceutic agent, and a number of other agents have also been tried. The most common route of administering pharmaceutic agents is through the mother and the placenta, although the direct administration of certain agents is becoming more common.

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Fetal surgical therapy has received international attention. The first successful repair of a diaphragmatic hernia in utero was the culmination of more than a decade of hard, tedious, and meticulous work.[1,2] There is still much work to be done developing surgical techniques, but the principles have been established.[3]

Despite the recent fanfare, fetal therapy is not new. Attempts to treat and reverse the abnormalities of fetal hemolytic disease came in the 1960s.[4] Intraperitoneal transfusions were used initially and by the 1970s had become a common form of intervention. In the late 1970s and throughout the 1980s, attempts at other surgical interventions of fetal disease, such as shunting obstructed bladders and hydrocephalus, and the first forays into open fetal surgery had been made.[2]

Although such dramatic fetal operations have received the most attention in the lay press, it should be recognized that some of the most important advances in fetal therapy have been pharmaceutic and that the future of fetal therapy will include the correction of genetic defects as well.[5(p236),6(p421)] We will review the spectrum of pharmaceutic interventions that reverse fetal structural abnormalities. We also will discuss the reduction of the incidence of neural tube defects with folic acid supplementation and strategies for preventing certain other structural anomalies. Finally, we will review the enhancement of fetal lung maturation with the use of corticosteroids and some proposed therapies for specific fetal biochemical alterations.

With the more advanced fetal diagnostic and interventional techniques, there is increased confidence about the ability to introduce agents into a fetus. The debate now moves to when and what to treat and, when treating with drugs, the best approach to administering them.

Transplacental Passage of Agents

Until recently the only approach to the pharmaceutic treatment of a fetus was transplacentally through the mother. With the introduction of high-resolution ultrasonography, the possibility of bypassing the placenta through direct invasive intra-amniotic, fetal intramuscular, or fetal intravenous administration has been realized and is being increasingly investigated.[7] The principal advantages of direct treatment are the avoidance of maternal toxicity and the metabolic effects of administered agents and the obviation of concern about the lack of placental permeability and transfer. It has been shown, for example, that the passage of cardiac agents across the placenta is less efficient in hydropic failure, thus rendering the sickest fetuses least likely to benefit (Table 1).[8]

When transfer characteristics of the intended therapeutic agents are favorable and possible maternal side effects are acceptable, the maternally administered transplacental route will probably continue to be the principal approach to fetal drug therapy. The efficiency with which a fetus can be so medicated will depend both on the rate of transfer of the drug from the mother to the fetus and the amount transferred after equilibrium across the placenta is reached. The placental transfer of pharmaceuticals and other chemicals is complex and remains an area of active investigation. The topic has been reviewed extensively by others[9,10] and will be only summarily discussed here.

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TABLE 1.—*Relative Advantages and Disadvantages of Transplacental and Direct Fetal Drug Therapy*

	Drug Route	
	Transplacental	*Direct*
Advantages		
Easy to give multiple doses		Bypasses "sick" placenta
Requires no procedural technical skill		Faster fetal uptake Can measure fetal levels
Disadvantages		
Dependent on placental function		Multiple invasive procedures
Maternal toxicity		Requires technical skill

Several experimental models, each having its own caveats, have been used in efforts to characterize the placental transfer of specific substances. The ideal model would be continuous concurrent in vivo pharmacokinetic evaluation of pregnant women and their fetuses after drug administration. Obviously such studies cannot be designed safely or ethically. Instead, for continuous and concurrent maternal-fetal drug evaluations, animal models have been substituted. The interpretation of data acquired from these studies, however, is limited by important differences in placental anatomy and maternal-fetal function between humans and available animals.[11] In vivo human studies have been restricted to efforts to measure maternal versus fetal blood concentrations of specific drugs either at the time of birth or during taking fetal blood specimens for other indications.[12] An alternative approach to evaluating human placental drug transfer is with in vitro preparations of dually perfused fresh human placenta.[13] This technique is hampered by the certainty of physiologic differences between a living intact placenta and an in vitro preparation regardless of how fresh.

The rate and extent of placental drug transfer varies considerably according to physiochemical properties of the substance and the complicated physiologic interaction of the fetal-maternal unit with the placenta at its interface (Table 2).[9] It is increasingly clear that essentially all exogenous substances including drugs, toxins, and nutrients are transferred to the developing embryo and fetus.[14] The common misconception of a "placental barrier" is outdated and misleading. Various specific transport systems operate across the placental exchange surface—active transport, facilitated transport, and pinocytosis—but simple diffusion is always involved and appears to be the principal mechanism for the transfer of most clinically relevant drugs.[9,10]

Fick's first law of diffusion,

$$\text{Rate of diffusion} = [K \times (C_m - C_f) \times \text{SA}]/d,$$

where K is the diffusion constant of the drug, $C_m - C_f$ represents the maternal-to-fetal concentration, SA is the exchange surface area, and d is the exchange membrane thickness, describes the relationships of the variables that govern the phenomenon of mass transfer by simple diffusion. From this equation it is apparent that placental drug transfer is driven by the principal force of a drug concentration gradient ($C_m - C_f$) across the exchange membrane. The rate of transfer is modified by placental characteristics (exchange surface area and thickness of the exchange surface membranes) and the physiochemical characteristics of the drug in question, which are represented by the diffusion constant K. Thus, a healthy placenta with a maximally intact exchange surface available and minimum diffusional distance will transfer a specific drug down a maternal-to-fetal concentration gradient much more efficiently than will a diseased placenta having either decreased exchange surface (perhaps due to multiple placental infarctions or the physiologic hypoperfusion that occurs in some hypertensive pregnant women) or increased diffusional distance (as may occur with placental edema in hydropic diseases). Similarly, a highly membrane-diffusible drug will be transported down a concentration gradient more effectively than will a less diffusible one.

The placental exchange surface can be thought of as a "lipoid barrier." Substances that are highly lipid-soluble tend to diffuse easily in a transcellular manner across the exchange membrane. In contrast, hydrophilic (water-soluble) substances are transferred poorly. The transfer of these drugs is negotiated through water-filled pores within the lipid membranes, a process that proves to be far less efficient. Other physiochemical characteristics of drugs that can profoundly influence placental transfer include molecular weight, ionization at maternal or fetal physiologic pH, and protein-binding characteristics.

Figure 1 shows four generalized models of maternal-to-fetal transplacental pharmacokinetics. Drugs having the properties of high lipid solubility, low ionization under physiologic conditions, and relatively low molecular mass (<1,000 daltons) will demonstrate rapid and exten-

TABLE 2.—*Principal Factors Influencing Transfer of Drugs From a Woman to Her Fetus*

Transfer	*Drug Factors*	*Placental Factors*	*Maternal Versus Fetal Factors*
Rate of transfer	Lipid solubility Molecular weight Protein binding	Exchange surface area Exchange membrane thickness Blood flow characteristics Type of transfer*	Maternal-to-fetal concentration gradient Maternal and fetal placental perfusion
Extent of transfer	Degree of ionization Protein binding	Type of transfer*	Maternal-to-fetal pH gradient Maternal versus fetal binding protein availability

*Passive diffusion is the principal mechanism of transfer, but facilitated and active transport mechanisms and pinocytosis may be involved in some cases.

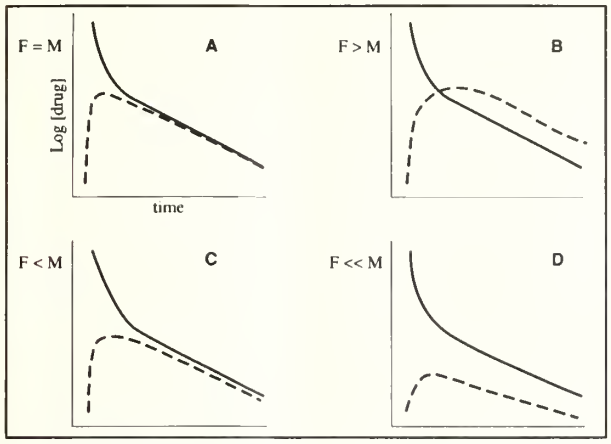

Figure 1.—The graphs represent 4 generalized models for fetal transplacental pharmacokinetics following a single maternal dose of prototype drugs: **A**, drugs in which fetal and maternal blood levels equilibrate; **B**, drugs in which fetal levels ultimately exceed maternal levels; **C**, drugs in which fetal levels are moderately or slightly less than maternal levels; and **D**, drugs in which fetal levels are nil or much less than maternal levels. See text for specific examples. Maternal blood levels are indicated by solid lines and fetal blood levels by broken lines.

sive transfer as shown in curve A. Examples of such drugs include most barbiturates, digoxin, phenytoins, ritodrine, and magnesium sulfate. Compounds that are hydrophilic, highly ionized, or of more substantial molecular weight (>1,000) will have much more limited rate and extent of placental transfer, as shown in curve B. Examples of such drugs are heparin (essentially "excluded" from exchange by its high molecular weight of approximately 1,200), quaternary ammonium compounds such as tubocurare, and succinylcholine (whose exchanges are profoundly limited by their high levels of ionization and water solubility), and erythromycin (exchange limited by high molecular weight and water solubility).

Other phenomena that can influence the ultimate transfer of certain drugs deserve mention. Placental metabolism could limit the transfer of an otherwise highly transferable compound. Cyclosporine, for example, is lipophilic but undergoes considerable metabolism during placental transfer, resulting in fetal concentrations about 50% of those of the mother. This drug would have a pharmacokinetic pattern as shown in curve C (Figure 1), despite its high membrane solubility. On the other hand, differential degrees of protein binding, or levels of drug ionization, in maternal versus fetal blood, as well as fetal urinary excretion with enteric recycling, can for some drugs result in fetal sequestration with levels actually exceeding those of the mother (as depicted in curve B). Examples of drugs sequestered by or of these mechanisms include penicillin, ampicillin, valproate, and many of the benzodiazepines.

Drug Treatment of Metabolic Defects

The potential for exogenous substances (drugs or ingested chemicals) to be transferred from a woman to her fetus is well known. In many cases, as with known teratogens such as thalidomide, phenytoin (Dilantin), and isotretinoin, the fetal effects can be adverse.[15] How the fetus responds to such exposures may be in part genetically determined.[16] Endogenous substances in the mother are likewise transferred to the fetus and in some cases may have similarly profound adverse fetal effects. Examples of fetal disorders caused by such "exposures" include diabetic embryopathy[17] and the extensive fetal damage seen due to untreated maternal phenylketonuria with resultant fetal hyperphenylalaninemia.[18]

For decades drugs and other products have been administered to pregnant women or directly to their fetuses in efforts to treat nonmetabolic fetal disorders or, in some cases, with the hope of improving the capacity for postnatal adaptation. Well-known examples include exchange transfusions for alloimmune hemolytic disease,* cardiac glycosides for fetal supraventricular tachycardia, and the administration of corticosteroids for the prevention of the respiratory distress syndrome in premature infants (discussed later in detail). There are few examples of attempts at the prenatal treatment of genetically determined metabolic defects, however. What follows is a discussion of three inborn metabolic errors affecting fetal development for which in utero fetal therapy has been attempted with varying success. We will also briefly discuss several animal models of unusual metabolic disorders for which novel antenatal therapies are being evaluated and that may someday be available for the treatment of affected human fetuses.

Congenital Adrenal Hyperplasia

The fetal adrenal glands can be pharmaceutically suppressed by maternal replacement doses of dexamethasone.[19] In congenital adrenal hyperplasia caused by 21-hydroxylase deficiency, there is impairment in the metabolic pathway from cholesterol to cortisol that creates both an excess of the metabolic intermediary 17-hydroxyprogesterone and a deficiency of cortisol. The excess 17-hydroxyprogesterone is metabolized by an alternative pathway, creating excessive androstenedione and other adrenal androgens. The absence of cortisol results in a lack of feedback inhibition of the hypothalamus, and high levels of corticotropin (ACTH) are produced. Elevated levels of corticotropin stimulate further activity in the adrenal gland and an exacerbation of the 17-hydroxyprogesterone excess, leading to still more adrenal androgen production. Consequently, genetic female fetuses are exposed to excess androgens and become masculinized. The abnormal genital differentiation can vary from clitoral hypertrophy to the complete formation of a phallus with an apparent scrotum.

In an attempt to prevent this defect, Evans and colleagues administered dexamethasone, a potent corticosteroid, to an at-risk mother beginning in the 10th week of gestation.[19] The rationale of such therapy was to replace feedback inhibition of the fetal hypothalamus, thereby eliminating excessive 17-hydroxyprogesterone production and the attendant overproduction of adrenal

*See K. J. Moise, Jr, MD, "Intrauterine Transfusion With Red Cells and Platelets," on pages 318-324.

androgen. Maternal estriol and cortisol levels indicated rapid and sustained fetal and maternal adrenal gland suppression. The fetus turned out to be a carrier.

Following these initial observations, Forest and David used the same protocol of administering 0.25 mg of dexamethasone orally to the mother four times a day beginning at 9 weeks' gestation to treat several fetuses.[20] They subsequently reported that the in utero dexamethasone-treated fetuses known to be clinically affected with the severe form of 21-hydroxylase-deficient adrenal hyperplasia were prevented from having external masculinization.[20,21] To date, several infants with classic congenital adrenal hyperplasia who clearly would have been masculinized have been born with normal genitalia. In a few cases, some masculinization has still been observed after this regimen was used beginning at 9 weeks. Our current protocol, therefore, is to begin at 7 weeks, although there have been too few cases to assess the results of this modification.[22,23] These events represent the first pharmacologic prevention of a birth defect and may serve as a model for other attempts at fetal therapy for congenital metabolic errors in which abnormal changes begin in utero.

Methylmalonic Acidemia

Methylmalonic acidemia is related to a functional vitamin B_{12} deficiency. Coenzymatically active vitamin B_{12} is required for the conversion of methylmalonyl coenzyme A to succinyl coenzyme A. Genetically determined causes of methylmalonic acidemia include defects in methylmalonyl-coenzyme A mutase or in the metabolism of vitamin B_{12} to the coenzymatically active form, adenocyanocobalamin, by the converting enzyme. Some patients may respond to the administration of large doses of B_{12}, which can enhance the amount of active holoenzyme (mutase apoenzyme plus adenocyanocobalamin).

Ampola and associates were the first to attempt antenatal therapy for a vitamin B_{12}-responsive variant of prenatally diagnosed fetal methylmalonic acidemia.[24] This disease in fetuses is known to be associated with increased methylmalonic acid excretion in maternal urine. Initial efforts to treat fetuses by high oral vitamin B_{12} intake in the mothers resulted in only marginally decreased maternal urinary methylmalonic acid excretion. When the intravenous administration of 5 mg of cyanocobalamin per day was introduced, however, there was a rise in maternal serum B_{12} levels to more than sixfold over normal, accompanied by a progressive decrease in maternal urinary methylmalonic acid excretion. In fact, maternal urinary methylmalonate levels were only slightly above the normal range when delivery occurred at 41 weeks' gestation. Amniotic fluid methylmalonic acid concentrations that were three times the normal mean at 19 weeks' gestation remained four times the normal mean at term, despite prenatal treatment.

In this instance, prenatal treatment certainly improved the fetal and secondarily the maternal biochemistry. Whether there was any notable clinical benefit to the fetus by in utero treatment cannot be assessed adequately. Reducing the fetal burden of methylmalonic acid should have some beneficial effect on fetal development and should reduce the risks in the neonatal period.[24,25] In the absence of further therapeutic trials, however, this remains only speculation.

Multiple Carboxylase Deficiency

Biotin-responsive multiple carboxylase deficiency is an inborn error of metabolism in which the mitochondrial biotin-dependent enzymes, pyruvate carboxylase, propionyl-coenzyme A carboxylase, and β-methylcrotonyl-coenzyme A carboxylase have diminished activity. Affected patients present as newborns or in the early childhood period with dermatitis, severe metabolic acidosis, and a characteristic pattern of organic acid excretion. Metabolism in patients or in their cultured cells can be restored toward normal with biotin supplementation. There have been two reports of the prenatal administration of biotin to fetuses affected with this disorder.[26,27] In both instances the oral administration of 10 mg per day of biotin to the mothers was followed by the delivery of homozygously affected neonates having no clinical or gross chemical abnormalities.

There is compelling evidence that biotin administration effectively prevents neonatal complications in certain patients with biotin-responsive multiple carboxylase deficiency. No maternal or fetal toxic effects from treatment were observed in either case.[26,27] It is not yet possible to assess definitively the relative advantages or disadvantages of prenatal treatment, although such therapy appears both effective and logical, and further trials seem warranted.

Abnormalities of Mineral Metabolism

The use of specific prenatal mineral supplementation has yet to be reported for the prevention of human fetal disease, but such additives have been used in animals with genetic deficiencies. These animal models are of considerable interest and suggest the possibility of therapy for analogous human genetic diseases.

Manganese. A number of genetic defects with associated pigmentary and inner ear abnormalities occur in animals. Some data suggest that manganese may play a role in modifying the expression of such defects.[28] Hurley and Bell have suggested that a sex-linked form of ocular albinism in humans, associated with labyrinthine dysfunction, may be analogous to some of these disorders in animals.[28] We are unaware of any studies of manganese metabolism in human ocular albinism or of attempts to administer manganese prenatally in the hope of ameliorating the expression of any associated labyrinthine defects.

Copper. Keen and colleagues have investigated the possible amelioration of deleterious effects, by prenatal copper administration, to mice with the autosomal recessive mutant "crinkled" gene.[29] These investigators have suggested that the crinkled gene produces many phenotypic characteristics common to patients with X-linked Menkes' kinky-hair syndrome. Dietary supplementation

of pregnant mice with copper sulfate partially reduced the anticipated phenotypic effects of the gene in homozygous offspring. As has been observed with Menkes' disease (which is refractory to postnatal therapy with copper), postnatal copper supplementation did not increase survival of the crinkled gene mutants. It is therefore conceivable that analogous to the observation of the amelioration of disease in crinkled mutants only by maternal copper supplementation throughout gestation, prenatal copper therapy may be of greater benefit to Menkes'-affected human fetuses as well.

Established Fetal Drug Therapies

Fetal Cardiac Therapy

Although great strides have been made in the diagnosis of fetal cardiac anatomical and functional abnormalities, in utero cardiac therapy currently is limited to the treatment of substantial arrhythmias. In the future, the treatment of some congenital anomalies, particularly valvular anomalies, may be attempted prenatally. The treatment of fetal arrhythmias has had considerable success and is discussed in more detail elsewhere.*

Folic Acid Supplementation and Prevention of Neural Tube Defects

In the United States, the reported overall incidence of neural tube defects ranges from 1 per 600 to nearly 1 per 1,000 live births, with a recurrence rate in first-degree relatives of 2% to 3%.[30(p223)]† Anencephaly is incompatible with life beyond early infancy, and cases of spina bifida are associated with a remarkable degree of morbidity and mortality.[31] With the exception of a small number of cases that can be attributed to pure genetic (mendelian syndromes) or chromosomal abnormalities, the specific pathogenesis of most cases remains unexplained. Epidemiologic data comparing the frequency of neural tube defects among genetically related persons with that of the general population point to a multifactorial model of pathogenesis. That is, there appears to be a genetic predisposition for neural tube defects that is profoundly influenced by environment. This nongenetic component to these disorders allows for the possibility of environmental modification to reduce the risk of these defects.

Epidemiologic studies have demonstrated a wide variation in the prevalence of neural tube defects among different countries, different social and ethnic groups, and from decade to decade in the same population. In many parts of the world, the birth prevalence of neural tube defects has been declining since the 1950s. In the United States, two birth defect surveillance systems, the Nationwide Birth Defect Monitoring Program and the Metropolitan Atlanta Congenital Defects Program, have found a decrease in the rate from 1.3 per 1,000 live births in 1970, to 0.6 per 1,000 births in 1989.[32] This decline strongly suggests the importance of an environmental cause. Several proposed explanations for the decline include population changes in the gene pool, improved and more widespread prenatal diagnostic facilities with selective abortion, and, of particular interest, better maternal nutrition. An association of dietary deficiencies with increased rates of neural tube defects was noted when food was scarce in post-World War II Germany and in Holland following the famine of 1944-1945. In England, the same association has been reported for the lower social classes in which diet was poor.

The possibility that folic acid might be involved was raised in the early 1960s when the administration of a folic acid-deficient diet combined with the folate antagonist, aminopterin, produced neural tube defects in animals. In addition, blood concentrations of folic acid, vitamin C, and vitamin B_{12} were found to be lower on average, and the quality of diet was found to be poorer, among women who gave birth to infants with neural tube defects. This evidence is nonspecific because a deficiency of one nutrient is correlated with the deficiency of other nutrients and of nonnutritional factors. In vitro studies with various nutrients found that only inositol was associated with neural tube defects. Therefore, no clear animal or in vitro evidence exists that vitamin supplementation protects against isolated cases of the disorder.

Human observational data that have been accumulating for the past decade have shown that taking vitamins, including folic acid, in the periconceptional period can reduce the incidence of neural tube defects. Published data are available from randomized and nonrandomized intervention trials and from observational studies. Early studies were conducted only in high-risk groups because of the rarity of the disease, and most of the data have been derived from England where the risk is substantially higher than in the United States. Most of the studies have been retrospective and their results inconclusive.

In 1980 and 1981 the results of two interventional studies were published in which vitamin supplementation around the time of conception was given to women who had a pregnancy with a neural tube defect. The South Wales study was a small, randomized trial of folic acid supplementation alone.[33] The study yielded inconclusive results when it was analyzed according to randomly allocated groups, but a significantly lower recurrence rate occurred in the supplemented group when randomization was ignored. In the second study, which was not randomized,[34] women were given a mixture of eight vitamins including folic acid (0.36 mg per day) in comparison with a control group of already-pregnant women who declined to take the vitamins. The study showed a sevenfold decreased ratio in risk between women taking supplements and those not taking them. This finding, while impressive, has been criticized because of self-selection of the women, an overrepresentation of high risk in the unsupplemented group, and an association between high social class and taking supplements. It therefore appeared that patient selection did introduce some bias to this multicenter study, but it is impossible to assess whether bias ex-

*See M. M. Brook, MD, N. H. Silverman, MD, and M. Villegas, "Cardiac Ultrasonography in Structural Abnormalities and Arrhythmias—Recognition and Treatment," on pages 286-300.

†See also N. C. Rose, MD, and M. T. Mennuti, MD, "Maternal Serum Screening for Neural Tube Defects and Fetal Chromosome Abnormalities," on pages 312-317.

plains all the results. There may also have been a direct preventive effect, and it was not known whether the responsible component was folic acid or one of the other vitamins.

Clearly there was a need to solve the problem by a large, randomized, double-blind intervention trial, which was launched in July 1983 by the British Medical Research Council and involved 33 centers.[35] The study was halted in 1991 by the ethical committee after abundant information and clear results were obtained on this issue, so that all women at risk could receive the possible benefits of the supplementation. The population tested was a high-risk group of women who had a previous pregnancy with a neural tube defect and who were randomly assigned to one of four supplementation groups: group A received 4.0 mg of folic acid, group B a multivitamin preparation also containing 4.0 mg of folic acid, group C neither multivitamins nor folic acid, and group D multivitamins without folic acid. To test the effect of folic acid, they compared the outcomes of groups A and B with those of groups C and D. To test the effect of multivitamins, the researchers compared the outcomes in groups B and D with those of groups A and C. The results of this study showed that high doses of folic acid reduced the risk of having a subsequent pregnancy with a neural tube defect by 70%, which is a threefold ratio. The study also showed that folic acid is an effective agent that avoids the need to use a mixture of vitamins with the concern over the possible toxicity of other vitamins.

Several relevant questions remain to be answered. No trial to date has been designed to demonstrate the relative efficacy of different doses or to answer the important question of what is the minimal effective dose of folic acid. Similarly, no present study has enough power to address the question of safety using high doses of folic acid for public health purposes.

The fact that 95% of the cases of neural tube defects occur in the low-risk general population raises the last and most important question: Are the results of studies restricted to the high-risk group (those mothers with a history of affected offspring) generalizable to the low-risk group? To determine whether periconceptional vitamin supplementation could reduce the incidence of a first occurrence of neural tube defects, four observational studies and one recent nonrandomized interventional Cuban study were done and the results published.[36-40] All but one showed a lower risk for the first occurrence of a neural tube defect in the general population for women who consumed 0.4 to 0.8 mg per day of folic acid from multivitamin supplementation, but all were criticized for possible selection and recall bias. Recently the results of a carefully designed, prospective, randomized controlled trial of multivitamin and mineral periconceptional supplementation (including 0.8 mg per day of folic acid) involving almost 5,000 Hungarian women who had not had a previous neural tube defect-affected pregnancy was reported.[41] This study was halted before its intended completion because of the clear evidence of a protective effect.

When data from several studies are synthesized, they suggest that folic acid alone at doses of 0.4 mg per day will reduce the risk of neural tube defects. The anticipated reduction in the United States has been reasonably estimated at 50%. Based on these data, the US Public Health Service has recommended that all women of childbearing age in the United States who are capable of becoming pregnant should consume 0.4 mg per day of folic acid for the purpose of reducing their risk of having a pregnancy affected with spina bifida or other neural tube defect.[42] Women who have had an affected pregnancy should consume 0.4 mg of folic acid per day, unless they are planning a pregnancy. In that case they can follow the August 1991 guideline from the Centers for Disease Control[43] and consult their physician about the desirability of using 4.0 mg of folic acid per day. This recommendation comes from the Medical Research Council data, which is felt to be the most rigorous study directed at this high-risk group and in which that was the only dose tested. Because of the well-known potential of high-dose folic acid supplementation to exacerbate the effect and to complicate the diagnosis of vitamin B_{12} deficiency, it has been suggested that the consumption of greater than 1 mg per day be carefully supervised by a physician.

Pharmaceutic Induction of Fetal Lung Maturity

Preterm delivery is a major cause of perinatal morbidity and mortality in the industrialized countries of the world. Despite recent advances in the respiratory care and management of premature infants, the respiratory distress syndrome is still a major cause of morbidity and mortality, including the sequelae of intracranial hemorrhage and chronic pulmonary disease.

Impaired or delayed surfactant synthesis appears central to the pathogenesis of the respiratory distress syndrome.[44] Various pharmaceutic agents are known to influence surfactant synthesis and possibly other aspects of lung development. These include corticosteroids, thyroid hormone, thyrotropin-releasing hormone (TRH), prolactin, insulin, aminophylline, and β-agonists. Since the introduction of surfactant to the arsenal of agents for the treatment and prevention of respiratory distress syndrome, it is now possible to combine hormonal therapy before delivery and surfactant administration after birth for the best possible drug intervention.

Corticosteroids

Corticosteroids have many effects on developing lungs. Some of the important ones evidenced by in vitro data and studies of animals are as follows:

- Increased synthesis of phosphatidylcholine (a major constituent of lung surfactant) and other phospholipids;
- Increased levels of surfactant apoproteins that have been documented to enhance surfactant reuse;
- Accelerated structural maturation of the fetal lung, as well as influence on lung collagen and elastin synthesis that may be responsible for improved lung distensibility;

- Increased β-receptor density in fetal lung;
- Decreased alveolar protein leak; and
- Increased pulmonary antioxidant enzyme activity that might have a protective effect on newborn lungs from oxygen toxicity.

Of several controlled randomized trials on the neonatal outcomes of corticosteroid administration before preterm delivery, the largest was from a collaborative group on antenatal steroid therapy in which 696 women at risk and their pregnancy outcomes were evaluated.[45] Most studies show similar results using dexamethasone, betamethasone, hydrocortisone, or methylprednisolone, although the first two agents were most commonly used. Accumulated data from the controlled trials, involving more than 3,000 participants, have shown that antenatal corticosteroid administration leads to a statistically significant and clinically relevant reduction in neonatal mortality and respiratory morbidity.[46] The beneficial effects have been manifested in babies at risk for the respiratory distress syndrome born at all gestational ages, whether or not there has been rupture of membranes.[47] Other benefits that appear to be associated with corticosteroid administration are reduced incidences of intraventricular hemorrhage, necrotizing enterocolitis, and neonatal death.

Several possible risks of high-dose corticosteroid therapy have been reported. The theoretical risk of maternal as well as fetal and neonatal infection may be increased if steroids are administered following prolonged rupture of membranes, although this has not been strongly apparent in studies addressing this issue.[46] An association of the development of pulmonary edema in pregnant women receiving a combination of steroids and tocolytic drugs has been reported.[48] There has also been a debate over a possible adverse effect of corticosteroid therapy on the evolution of preeclampsia.[49] In summary, however, with proper patient selection and intensive antenatal and neonatal care, most investigators believe that the demonstrated advantages of antenatal steroid therapy outweigh the mostly theoretical risks.

Thyroid Hormones

Thyroid hormones play a role in fetal lung maturation. From studies of animals it appears that thyroid hormones increase surfactant synthesis, accelerate the structural development of the lungs, decrease the alveolar capillary protein leak, and generally improve lung function. Because thyroxine and triiodothyronine are poorly transported across the placenta, intra-amniotic instillation of thyroxine has been used in clinical trials with promising results.[50] This approach relies on fetal absorption, however (which depends on fetal swallowing and amniotic fluid volume), making dosimetry problematic.

A second approach involves stimulating endogenous fetal production of triiodothyronine and thyroxine by thyrotropin-releasing hormone, which is known to readily cross the placenta. An added possible benefit of exogenous TRH is its ability to stimulate fetal prolactin production. Prolactin has been reported to have its own potentiating effect on fetal lung maturation. With this rationale, a randomized study has been published on the combined use of corticosteroids and TRH compared with corticosteroids alone.[51] Combined therapy was associated with a greater rate of post-therapy improvement in the lecithin-sphingomyelin ratio, significantly decreased the number of days in the neonatal period requiring respiratory support, and lowered the incidence of bronchopulmonary dysplasia. Although this report is encouraging, additional studies are needed to confirm and characterize the effect before thyroid hormones are likely to be widely accepted.

Other Agents Affecting Fetal Lung Maturation

Aminophylline. In vitro studies and those in animals have shown positive effects of aminophylline on fetal lung maturation. Clinical trials are limited, although one study reported a reduced incidence of the respiratory distress syndrome in newborns of aminophylline-treated mothers compared with a control group.[52] Further studies are needed before any conclusion can be made.

β-Adrenergic agents. There is some evidence that β-adrenergic stimulation enhances surfactant secretion from type II alveolar cells of the fetal lung. Because these agents are so extensively used in obstetrics to inhibit preterm labor, it is difficult to assess their additional benefit in preventing the respiratory distress syndrome.

Ambroxol. Ambroxol, a benzydamine, was developed as a pulmonary expectorant and is widely used in Europe. Its use has been shown to stimulate surfactant production and secretion by type II alveolar cells, although its mechanism of action is not completely understood. A multicenter, randomized Italian study compared antenatal therapy using betamethasone with that of ambroxol for the prevention of the respiratory distress syndrome.[53] The incidence of the disorder was 13% in the ambroxol-treated group compared with 31% in the group receiving betamethasone. The authors concluded that ambroxol is at least as effective as steroids for preventing the respiratory distress syndrome. Further clinical and experimental evaluation of this promising drug is needed and ongoing.

The Future

Advances in technology, while not entirely predictable, can be expected to produce new therapeutic agents for the treatment of cardiac arrhythmias, more precise biologic replacement levels of missing hormones such as in 21-hydroxylase-deficient congenital adrenal hyperplasia, vitamin and mineral supplements for a number of disorders, and improved steroid therapy for fetal lung maturation. The concomitant developments of enhanced surgical techniques and molecular genetic diagnosis make it likely that there will be improved access to fetuses and more precise diagnoses available that will allow for targeted treatments using all three approaches: surgical, drug, and genetic. The future appears bright, although it is impossible to predict the rate at which each of these areas will develop.

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Nonvascular Needle and Shunt Placements for Fetal Therapy

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The nonvascular placement of needles and shunts for the in utero treatment of fetuses with fluid-filled, space-occupying anomalies has been done for about 10 years. The rationale for this approach is to attempt to prevent progressive impairment of organ function or lethal damage by early decompression. Experience has taught us that the key to success in these cases is the exclusion of associated anomalies and the use of appropriate tests to assess the residual organ function at the time of first diagnosis. In fetuses with hydrothorax, shunts can prevent pulmonary hypoplasia, and in those with obstructive uropathy, they can prevent the development of progressive lung hypoplasia and renal damage before a fetus is fully viable. In fetuses with ovarian cysts, prenatal puncture is occasionally indicated, but in those with hydrocephalus, the beneficial effect of prenatal drainage is more controversial. The catheters used for in utero placement have been improved and carry a smaller risk than open fetal surgical procedures.

(Holzgreve W, Evans MI: Nonvascular needle and shunt placements for fetal therapy, *In* Fetal Medicine [Special Issue]. West J Med 1993; 159:333-340)

In 1985 Golbus of the University of California, San Francisco, one of the pioneers of fetal therapy, wrote as the guest editor of *Seminars in Perinatology* the following[1(p51)]:

> In utero fetal therapy remains an experimental form of fetal medicine. Thus, it is very important that these approaches to in utero evaluation and management not be applied to the general care of obstetric patients. Fetal therapy should only be offered in centers where ongoing research is being done and where the multidisciplinary team approach to these problems is available.

This concept is still true almost ten years later, particularly in the area of nonvascular needle and shunt placement for in utero treatment. The percutaneous placement of umbilical needles for prenatal diagnosis and therapy is covered elsewhere in this issue.* This contribution, therefore, deals only with the in utero treatment of obstructive uropathy, hydrothorax, hydrocephalus, and ovarian cysts.

In a recent review we summarized the general questions that have to be addressed before contemplating any needle or shunt placement in utero[2]:

- What is the natural outcome of this anomaly? Will additional or irreversible damage be caused to the fetus if repair procedures are delayed until after birth?
- Is it possible to correct the anomaly or its consequences in utero? Will the procedure change the natural outcome?
- What is the risk to the mother and the fetus?

Surgical intervention in utero should be considered only if the natural history of the anomaly is frequently associated with neonatal severe handicap or early death; there is evidence (from animal models) that the natural history can be changed by the surgical procedure; and the risk to the mother is relatively small, as proved in a rigorous study of animals (such as nonhuman primates).

Intrauterine Obstructive Uropathy

The widespread use of modern grey-scale ultrasonography in obstetrics has permitted the recognition of obstructive uropathies more frequently and earlier in pregnancy than previously possible. Obstructive uropathies must be differentiated from a variety of mainly cystic congenital disorders of the fetus. Several reports have addressed the poor prognosis of fetuses with persistent urinary obstruction, particularly with oligohydramnios and resultant pulmonary hypoplasia.[3,4] The prognosis for fetuses with persistent obstruction is poor because the backup of urine can both destroy the renal parenchyma and impede pulmonary development.[5,6] Retrograde pressure forms behind the obstruction and causes increasing dilation of the urinary system.[3] As documented in studies of animals, hydronephrotic and, perhaps, dysplastic changes occur in the renal parenchyma.[7] The severe oligohydramnios associated with bilateral urinary tract obstruction can

*See K. J. Moise, Jr, MD, "Intrauterine Transfusion With Red Cells and Platelets," on pages 318-324.

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result in pressure deformities of the face and limbs and pulmonary hypoplasia, the so-called Potter sequence. Neonatal death is often caused by respiratory tract insufficiency. The timing and the degree of obstruction are crucial determinants in the development of irreversible renal and pulmonary damage.[7-9]

Several indices have been used in the prenatal evaluation of renal function in fetuses with obstructive uropathy, including the amniotic fluid volume, the ultrasonographic appearance of the kidneys, and the biochemical composition of the fetal urine. In cases of severe urethral obstruction, the bladder can be profoundly distended (Figure 1), often associated with enlarged renal pelvises. Because sonography is especially accurate for detecting fluid-filled abnormal lesions, fetal urinary tract obstruction can easily be detected prenatally.[10] In cases of fetal urethral obstruction, the characteristic sonographic finding is the dilation of both the fetal urinary tract and the proximal urethra, resulting in a "keyhole" appearance,[11,12] usually in a male fetus. Even in cases of urethral or bladder outlet

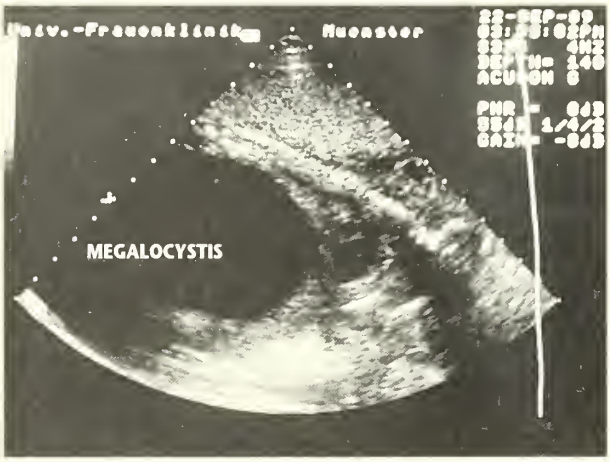

Figure 1.—The ultrasonogram shows a fetus with urethral obstruction and a grossly distended bladder (megalocystis) pushing the diaphragm upwards.

obstruction where a symmetric back-up pressure might be expected with uniform degrees of hydronephrosis in both kidneys, there is often considerable asymmetry in the degree of hydronephrosis of the kidneys.

Megalocystis and hydronephrosis as the first signs of obstructive uropathy can develop early in pregnancy, and they can be associated late in the first or early in the second trimester with severe oligohydramnios, but also with normal amounts of amniotic fluid. Wladimiroff and coworkers pointed out, however, on the basis of findings of weekly ultrasonograms in one patient, that slight bilateral hydronephrosis as a first sign of obstructive uropathy due to urethral valves could not be established before 30 weeks' gestation, although anuria developed and bilateral ureterocutaneostomy had to be carried out postnatally.[13] On the other hand, cases of transient in utero hydronephrosis have also been reported,[14,15] some of which possibly being due to fetal vesicoureteral reflux resolving in the course of maturation.

Besides urethral obstructions, ureteropelvic junction obstruction is the most common cause of hydronephrosis in neonates and children.[16] These cases can be differentiated prenatally because hydronephrosis is not associated with megalocystis as opposed to urethral obstruction.

It is difficult to quantify prenatally the degree of hydronephrosis. To facilitate communication and comparison of results in the literature, Grignon and associates proposed a morphologic classification of in utero urinary tract dilation.[17] They suggested that grade 1 dilation (anteroposterior diameter of the renal pelvis less than 10 mm) should be considered normal, whereas grades 2 and 3 with intermediate hydronephrosis require postnatal urologic surgical therapy in nearly half the cases. Grade 4, moderate dilation of the calyces with easily identified residual renal cortex, and grade 5, severe dilation of the calyces with atrophic cortex, were clearly considered serious disorders requiring a neonatal corrective operation. This classification may be helpful for communication, but because of the variability of the clinical course of fetal obstructive uropathies, any classification scheme is problematic.

For practical purposes, the systematic evaluation of fetal obstructive uropathies by Filly and colleagues provided valuable information—that cortical cysts had a sensitivity of 44% and a specificity of 100% in predicting renal dysplasia, whereas increased echogenicity had a sensitivity of only 57% and a specificity of 89%.[18,19] The severity of hydronephrosis was least predictive, with a sensitivity of 35% and a specificity of 78%. Therefore, the power of ultrasonography to assess the degree of renal residual function after the prenatal detection of bilateral hydronephrosis is still limited, even with the use of the best machines with high resolution.

Neither does the degree of dilation of the ureters correlate well with the degree of renal damage.[20] We share the experience of the Fetal Treatment Program in San Francisco that fetal kidneys that are obstructed severely enough to result in rupture of the collecting system and the formation of a perinephric urinoma and urinary ascites are unlikely to have adequate residual renal function.[21]

It remains to be investigated systematically whether the use of Doppler studies on the renal artery flow, which is now greatly aided by the introduction of color-coded Doppler sonography, can be helpful for the much-needed improvement of the prenatal assessment of kidney function in urinary tract obstruction. The hypothesis regarding the Doppler evaluation of the renal artery flow is that an increased resistance index correlates with the degree of parenchymal compression and subsequently with the degree of renal insufficiency.

Assessment of Fetal Renal Function In Utero

Because in cases with sonographically recognized obstructive uropathies ultrasonography cannot identify all dysplastic kidneys, biochemical studies from fetal urine specimens were done by the San Francisco Fetal Treat-

ment Group.[19] Fetal urine is known to be produced from the 13th week of gestation onwards and is an ultrafiltrate of fetal serum made hypotonic by selective tubular absorption of sodium and chloride. In addition to this, it has been determined that the normal levels of sodium and chloride fall throughout gestation.[22] For example, a sodium level of 120 mmol per liter in fetal urine is still in the normal range at 15 weeks but clearly abnormal after 20 weeks' gestation.

In a retrospective analysis of fetal urine specimens in San Francisco, it was found that fetuses with hypotonic urine had later been found to have good renal function as opposed to those with isotonic urine, who later had poor renal function. Urine osmolarity had a similar predictive value. In summary, the San Francisco retrospective study revealed that urinary sodium levels above 100 mmol per liter, chloride levels above 90 mmol per liter, and osmolarity above 210 mOsm were associated with insufficient tubular reabsorption capacity and irreversibly damaged renal function at birth.

Lenz and co-workers showed that, as with plasma values, concentrations of neutral amnio acids in the fetal urine are also predictive of irreversibly destroyed kidneys because they reflect poor tubular capacity.[23] Later Nicolini and associates pointed out that the selection of fetuses for vesicoamniotic shunting can be further improved by serial sampling of each kidney separately.[24]

Like others,[25,26] however, we found that these useful variables are not always able to correctly select those cases in which drainage of the obstructed urinary tract might be beneficial. We therefore looked for additional determinants to improve the prenatal prediction about the renal function.[27]

In the postnatal and the prenatal periods, proteinuria in the course of renal disease is caused either by a disease process in the glomeruli or by damage in the tubular reabsorption capacity. Because this pathogenetic difference is expressed by the molecular weight of the proteins,[28] the site and degree of the underlying lesions in kidneys with pathologic proteinuria can be identified by separating urinary proteins on polyacrylamide gel electrophoresis with sodium dodecyl sulfate as detergent (SDS-PAGE). Molecules between 10 and 200×10^3 daltons can be separated and stained with Amidoblack by this technique. An increase in micromolecular proteins (molecular weight < 70,000) is indicative of an impairment in tubular reabsorption of those proteins that normally pass almost freely through the glomeruli.[29] The SDS-PAGE method not only separates proteins according to their molecular weight, but also allows their quantity to be estimated. In normal pregnancies at 18 weeks, no proteins other than albumin are found in fetal urine (Figure 2).

Using this new test we reported the successful shunting of a fetus with megalocystis and associated anhydramnios at 19 weeks' gestation in which urinary electrolytes and osmolarity were compatible with severe renal damage. Adding protein analysis by SDS-PAGE supported the prediction of a good outcome after shunt treatment and subsequent delivery at 36 weeks' gestation.[30]

Figure 2.—A fetal urine specimen obtained at 19 weeks' gestation was analyzed using polyacrylamide gel electrophoresis with sodium dodecyl sulfate. The fat band in the upper part of the panel represents albumin. Severe tubular damage is indicated by the presence of microprotein bands in the lower half of the gel.

Subsequently we used the SDS-PAGE method in utero, together with the San Francisco profile (modified for gestational age) in a series of 21 cases.[31] We found in this group of patients that the electrolyte and osmolarity evaluations were incorrect in four instances, whereas the SDS-PAGE results were in agreement with the ultimate outcome of the pregnancy in all of these cases. We therefore suggest that the SDS-PAGE evaluation should be added to previously described fetal urinary function tests in cases of severe and progressive urinary tract obstructions before decisions about the prenatal management are made.

In utero treatment should be reserved for fetuses with bilateral urinary tract obstruction, maintained renal function, decreased amniotic fluid volume, and no other life-threatening anomalies. Cytogenetic anomalies and congenital malformations of other systems are diagnosed in 15% to 40% of cases of fetal obstructive uropathy. The evaluation should include the karyotype (by amniocentesis, placental biopsy, or cordocentesis), echocardiography, and a detailed ultrasound examination to assess renal size or dysplastic changes and to evaluate fetal bladder filling.[9] The patterns of chromosomal abnormalities were related to the different types of renal defects. In mild hydronephrosis, the most common chromosome abnormality was trisomy 21, whereas in moderate to severe hydronephrosis, multicystic kidneys, or renal agenesis, the most common abnormalities were trisomies 18 and 13. If fetal visualization is impaired by severe oligohydramnios, the artificial installation of fluid will improve sonographic visibility. The observation of fetal behavior (drinking, filling of stomach and bladder) makes the study of fetal anatomy more accurate.

Most procedures of vesicoamniotic shunt placement have been done percutaneously with ultrasonographic guidance.[9] A double-coiled nylon catheter has been used

in most cases, with good results. One-way valve catheters are not necessary because the pressure in the obstructed bladder usually exceeds that in the amniotic fluid, and there are adverse consequences if amniotic fluid goes into the bladder.

The fetal surgery registry coordinated by Frank Manning, MD, of the University of Manitoba, Canada, lists 98 cases as of March 1993 treated by indwelling shunts.[2] The longest follow-up is more than 11 years, and the overall survival has been 41%. Particularly at the beginning of the series, a number of patients were inappropriately chosen for surgical therapy, which considerably lowered the survival statistics. For example, several fetuses had a shunt placed before a chromosome abnormality was elucidated. When appropriately stratified by cause, survival reaches as much as 70% for male fetuses with a posterior urethral valve.

Shunt Procedures

The transabdominal percutaneous intrauterine placing of a suprapubic bladder shunt is currently mainly done by using a Rocket shunt technique as developed by Rodeck (Figure 3).[32] After a directional approach has been chosen, the maternal skin is prepared, and a scalpel blade is used to nick the maternal skin. The shunt loader is then inserted into the uterine cavity and suprapubically into the fetal bladder. After this the trocar is removed. A plastic double pigtailed catheter with a central wire stylet is inserted the entire length of the catheter. The wire stylet is then removed. A short plunger is used to push the distal half of the catheter into the fetal bladder. A long plunger is inserted down the shaft to touch the proximal end of the catheter. The outer tube is then pulled back while holding the plunger steady, resulting in the proximal half of the catheter being dropped into the amniotic cavity.

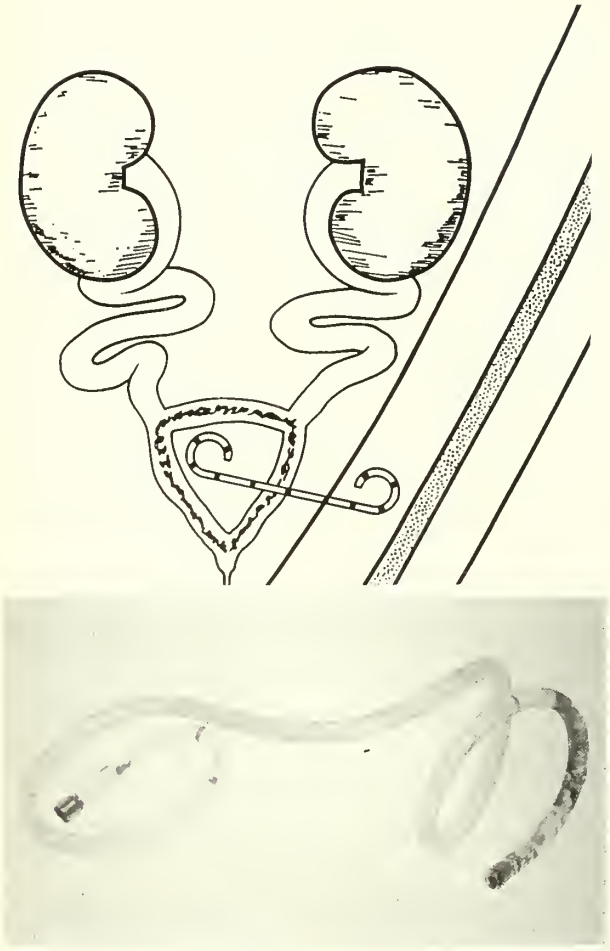

Figure 3.—A vesicoamniotic catheter is used in fetal obstructive uropathy. **Top,** A schematic depicts the in utero placement of the catheter in the fetal bladder. **Bottom,** The Rodeck shunt is shown after postnatal removal from an infant who had the shunt placed in utero.

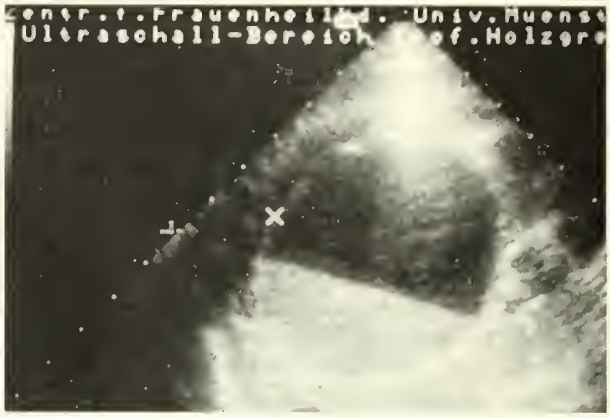

Figure 4.—The sonogram shows the typical appearance of fetal ovarian cysts with sedimented cells in the lower part of the cysts.

Patients who have undergone successful shunting procedures are a testimonial to the possible benefit of early, aggressive evaluation of fetal renal function and for successful fetal treatment in a few selected cases of obstructive uropathies.

With more advanced ultrasonograms and biochemical tests, it is obvious that most of the initial early attempts at fetal urinary diversion were performed on poorly chosen patients. We now need to start afresh in creating a data base to evaluate the natural history, function, and possibilities for intervention by vesicoamniotic shunt placement.

Management of Fetal Ovarian Cysts In Utero

Although it is known from autopsy specimens of stillbirths and neonates that small follicular cysts are not unusual in full-term infants, large cysts are only rarely noted clinically or by sonography.[33] The diagnosis can be suspected prenatally if a cystic lesion is visualized next to a kidney in a female fetus (Figure 4). Prenatally these cysts are usually uncomplicated and often disappear spontaneously after delivery, but sometimes they require surgical intervention because of their size or secondary complications.[34,35] If they are taken out by laparotomy in the neonatal period it is difficult even with microsurgery not to harm the small ovary, which is often intimately integrated into the wall of the cyst. It therefore seems pru-

dent either to allow even large cysts to regress spontaneously or to decompress those that are causing complications.

From our own experience with 13 such cases, we know that complications can occur prenatally from tor-

Figure 5.—In utero torsion of a fetal ovarian cyst is seen on the sonogram, which shows the inhomogeneous internal structure.

sion of the pedicle and subsequent necrosis or hemorrhage into the cyst (Figure 5). Therefore, we recommend prenatal decompression especially if the cyst is large and is a "wandering mass."

High levels of prostaglandin E_2, progesterone, and testosterone in the cystic fluid confirm the diagnosis after prenatal puncture. The differential diagnosis includes choledochal,[36] paranephric, sacrococcygeal, mesenteric, and urachal cysts. The precise topography aided by color-coded Doppler mapping of the vasculature can be helpful in the differential diagnosis.

In summary, the general approach to fetal ovarian cysts in utero is conservative, but in special cases prenatal decompression seems useful for improving the outcome.

Management of Ventriculomegaly In Utero

In the early 1980s much of the focus regarding the potential for fetal therapy centered on obstructive ventriculomegaly. Interest in this disorder emerged from the relative ease of diagnosis by ultrasonography and was amplified by the success rates of shunting procedures performed in neonates. The concept, as developed in animal models, was that early shunting of ventriculomegaly in utero might prevent the irreversible damage caused by prolonged increased intracranial pressure. The original ventriculoamniotic shunt for prenatal placement was developed about ten years ago by Clewell and co-workers in Denver, Colorado, and also applied first by this group in utero.[37]

In humans the experience with ventriculoamniotic shunts seems at first glance to be disappointing. As of July 1993, less than 50 cases of fetal ventriculomegaly treated in utero by ventriculoamniotic shunts were reported to the International Fetal Registry.[38] In most instances, the shunting was performed in fetuses presumed to have ventriculomegaly or hydrocephalus due to aqueductal stenosis. The mean gestational age at diagnosis was 25 ± 2.73 weeks (range, 18 to 31), and the mean age at treatment was 27 ± 2.6 weeks (range, 23 to 33). The duration of effective therapy cannot be determined from registry data because objective means for assessing shunt function are not available. Of 41 fetuses with hydrocephalus treated by ventriculoamniotic shunting, 34 survived. Of the 7 deaths that occurred, 4 could be directly attributed to trauma at the time of the shunt placement or to premature labor occurring within 48 hours of shunt placement. Thus, the crude mortality rate for the procedure is about 9%. The 34 surviving infants have been observed on average for 12.2 ± 5.8 months (range, 6 to 36). Of these, 14, all with aqueductal stenosis, are thus far reported as normal at follow-up evaluation. The remaining survivors all showed varying degrees of neurologic handicap, and most of the children (18 of 34 survivors, 53%) are classified as having severe handicaps. These infants all exhibit gross delay in reaching developmental milestones, and in infants, the tested developmental quotient was always less than 60. Five of these infants have cortical blindness, three have seizure disorders, and two have spastic diplegia. The outcome among survivors was related principally to the primary cause of obstructive hydrocephalus. Aqueductal stenosis of uncertain cause was the most common etiologic factor for obstructive hydrocephalus (28 of 41 cases, 68%), and the only intact survivors are found in this group.

The results of ventriculoamniotic shunting for fetal ventriculomegaly have been disappointing,[39] and consequently there has been a de facto moratorium in place since the early 1980s.[2] The hope of selecting fetuses who otherwise would be severely impaired by ventriculomegaly and of avoiding irreversible damage by intrauterine treatment was substituted in a few instances with the survival of severely affected infants who otherwise would have died. In addition to the poor outcomes in treated fetuses, abandonment of the concept of shunting for ventriculomegaly must be considered for several reasons.[40] Analysis of the cases of ventriculoamniotic shunt placement performed in the 1980s and reported in the registry shows that selection criteria were not always employed appropriately, and fetuses with ventriculomegaly associated with other severe anomalies (such as holoprosencephaly or autosomal trisomies) also were given the benefit of intrauterine treatment.

Our own experience and current reports demonstrate that the natural history of fetal ventriculomegaly is poor in general.[40] The major determinant of the prognosis was the association with other intracranial or extracranial malformations. Additional malformations affect 70% to 85% of fetuses with ventriculomegaly, and all such cases suffer perinatal mortality or severe morbidity. Even if a diligent search for additional malformations was performed by combining a detailed ultrasound study of the fetus with

amniocentesis for karyotyping and amniotic fluid α-fetoprotein and acetylcholinesterase assessment, as much as 40% of abnormalities would not be detected, even by experienced personnel.

The apparently obvious candidates for in utero ventricular shunting are the fetuses with isolated progressive obstructive ventriculomegaly as opposed to asymmetric hydrocephalus due to primary brain malformation (Figure 6). The number of cases is limited by a high rate of associated anomalies and by the relative failure to exclude additional malformations prenatally. The severity of ventriculomegaly is not always predictive of outcome or even of the need for postnatal shunt, as ventriculomegaly may not be associated with elevated intracranial pressure.

Considering the uncertainty and the difficulty of an accurate prenatal diagnosis, the intrauterine treatment of fetal ventriculomegaly remains a controversial and highly experimental procedure that is currently moribund because of the moratorium. When the option in midtrimester, however, is between terminating the pregnancy or simply observing the progressive dilation of the ventricles, the placement of a ventriculoamniotic shunt should present a third option in selected cases. Given the few good candidates and the need to develop a new catheter

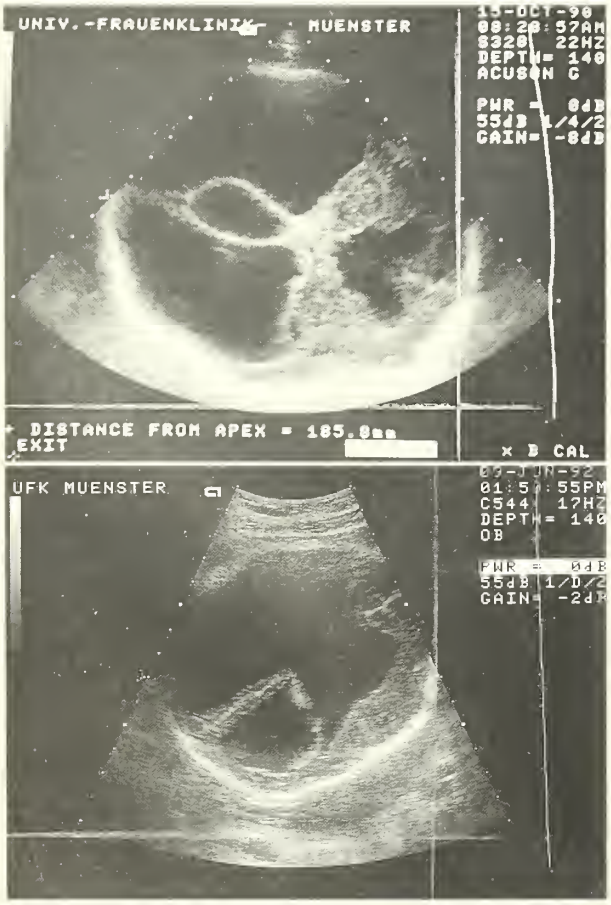

Figure 6.—**Top,** A symmetric type of hydrocephalus due to aqueductal stenosis is shown. **Bottom,** The sonogram shows the asymmetric type of hydrocephalus due to primary brain malformation.

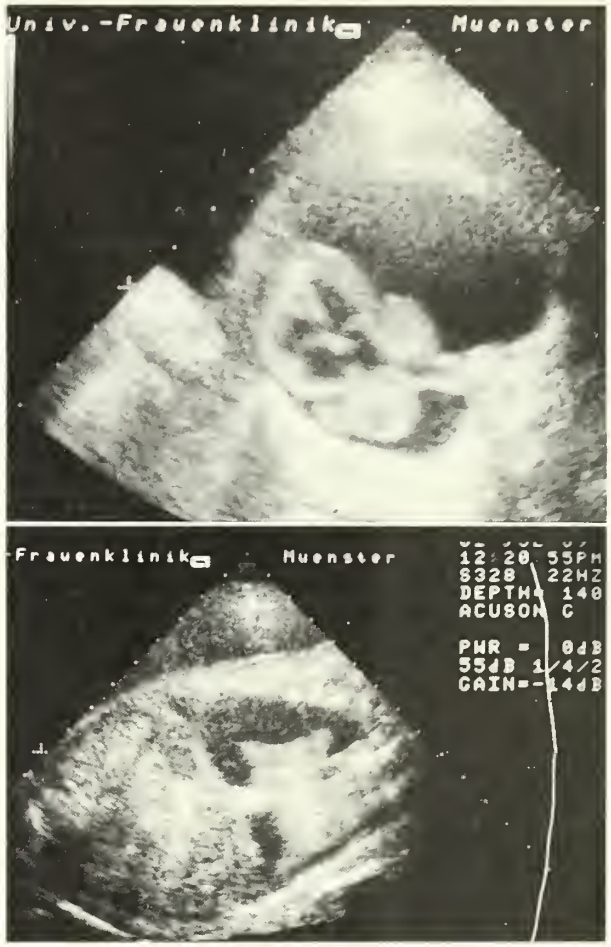

Figure 7.—The grey-scale sonograms reveal fetal hydrothorax: **top,** a transverse section; **bottom,** a longitudinal section.

(as none is currently available), a carefully designed study should be performed in one of the few centers experienced in the technical aspects of ventriculoamniotic shunt placement to settle the question of its usefulness.

Thoracoamniotic Shunting

Intrauterine mediastinal compression by conditions such as cystic adenomatoid malformation and pleural effusions can lead to the development of hydrops and polyhydramnios, which are associated with a high risk of premature delivery and intrauterine or neonatal demise.

Isolated pleural effusions (hydrothorax) in the fetus either may resolve spontaneously or may be treated effectively after birth. In some cases, however, severe and chronic compression of the fetal lungs in utero can result in pulmonary hypoplasia and neonatal death. In others, mediastinal compression leads to the development of hydrops and polyhydramnios, which are associated with a high risk of premature delivery and perinatal death. Fetal hydrothorax can be visualized well in utero by grey-scale sonography (Figure 7).

The data from fetuses with isolated pleural or pericardial effusions suggest that certainly in some cases short-term decompression by thoracocentesis or temporary

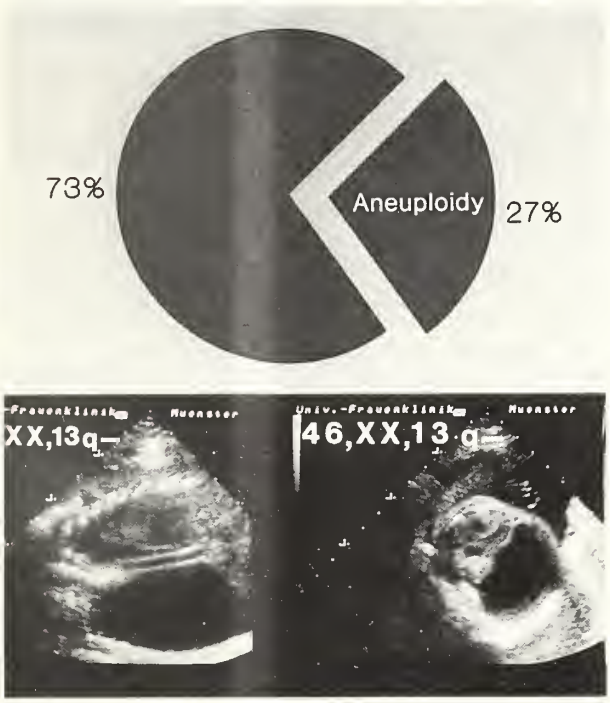

Figure 8.—Chromosomal disorders are shown in cases of fetal hydrothorax. **Top,** the rate of aneuploidies in a series of 22 cases is illustrated; 6 patients were affected. **Bottom,** The ultrasonograms are of fetuses with hydrothorax and a structural chromosomal abnormality.

drainage may disrupt the underlying disorder. In most cases, however, the fluid reaccumulates within 24 hours, requiring repeated procedures that are likely to be more traumatic than thoracoamniotic shunting.

The data collected by Nicolaides and associates indicate that thoracoamniotic shunting is useful for the diagnostic evaluation of fetuses with abnormal collections of intrathoracic fluid.[2] First, the diagnosis of an underlying cardiac abnormality or other intrathoracic lesion may become apparent only after effective decompression and return of the mediastinum to its normal position. It can also be useful in the prenatal diagnosis of pulmonary hypoplasia because in such cases, the lungs often fail to expand after shunting. Furthermore, it may help to distinguish between hydrops due to the primary accumulation of pleural effusions, in which the ascites and skin edema may resolve after shunting, and other causes of hydrops, such as infection, in which drainage of the effusions does not prevent worsening of the hydrops.

Thoracoamniotic shunting is also an effective and apparently safe method of the ongoing drainage of fetal pleural effusions or pulmonary cysts in utero. It can reverse fetal hydrops, resolve polyhydramnios and thereby reduce the risk of preterm delivery, and, most important, it may prevent pulmonary hypoplasia. The alternative management of pleural effusions by thoracocentesis immediately before or after delivery could prevent respiratory distress in the neonate if this is the result of simple mechanical compression of otherwise normally developed lungs. Such treatment would not prevent pulmonary hypoplasia due to prolonged intrathoracic compression or, indeed, progressive disease from pleural effusions to hydrops fetalis and intrauterine death. Moreover, in a proportion of hydropic fetuses, thoracoamniotic shunting does not prevent their death due to the underlying disease causing the hydrops. Similar to the other malformations discussed here, prenatal karyotyping also needs to be done before any in utero shunt placement, because the rate of aneuploidies and structural chromosomal anomalies (Figure 8) is high. Karyotyping often can be performed from lymphocytes out of the pleural effusion fluid after the initial percutaneous umbilical sampling.

In summary, whereas the percutaneous approach under ultrasonographic guidance seems to be the preferred method for placing a shunt in a hollow enlarged viscus, the correction of more extensive fetal anomalies such as diaphragmatic hernia or large adenomatoid lung malformation might require more extensive and more invasive operations on both mother and fetus ("open surgery").[41] With improved quality of the catheters for in utero placement and a lower risk of obstruction, displacement, and other complications, the significantly higher risk of open fetal operations needs even stronger justification. About ten years after the initial nonvascular shunt placement in utero by the San Francisco Fetal Treatment Group, worldwide experience has shown that surgical intervention is indicated only in a small group of carefully selected fetuses without lethal associated malformations but with progressive sequelae from isolated obstruction before viability.

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Fetal Surgery

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While most prenatally diagnosed malformations are best managed by appropriate medical and surgical therapy after birth, a few may require or benefit from correction before birth. Extensive experimental work in animals and innovative technologic developments have made fetal surgery a viable approach to perinatal care. Managing preterm labor continues to be a vexing problem. At present, only a few life-threatening malformations have been successfully corrected. Additional research into the abnormal function of some malformations, the development of less interventional techniques, and fetal stem cell transplantation should lead to successful treatment of more fetal disorders.

(Harrison MR: Fetal surgery, *In* Fetal Medicine [Special Issue]. West J Med 1993; 159:341-349)

As the veil of mystery is stripped from the once-secretive fetus by powerful new imaging and sampling techniques, prenatal treatment is emerging as the logical consequence of prenatal diagnosis. Although most prenatally diagnosed malformations are best managed by appropriate medical and surgical therapy after maternal transport and planned delivery near term, a few simple anatomic abnormalities with predictable developmental consequences may require correction before birth. In the 1980s the developmental function of several potentially correctable lesions was worked out in animal models, the natural history of these anomalies was determined by the serial observation of human fetuses, and selection criteria for intervention were developed.[1,2] The anesthetic, tocolytic, and surgical techniques for hysterotomy and fetal surgery were developed experimentally and introduced clinically.[3,4] In the 1990s, this investment in basic and clinical research will benefit an increasing number of fetuses.

Although only a few fetal defects are amenable to surgical treatment at present, the enterprise of fetal surgery has produced some unexpected spin-offs that have interest beyond this narrow therapeutic field. For pediatricians, neonatologists, and dysmorphologists, the natural history and abnormal function of many previously mysterious newborn conditions have been clarified by following the development of the disease in utero. For several diseases, such as diaphragmatic hernia, cystic adenomatoid malformation, and cystic hygroma, the outcome is worse when detected in a fetus than when the same disease is diagnosed after birth, due to a "hidden mortality" arising from previously unrecognized in utero demise or "stillbirth."[5] For obstetricians, perinatologists, and fetologists, many formidable technical problems in obtaining access to a fetus have been solved. Extensive experimental work in fetal lambs and monkeys has allowed the development of techniques for opening and closing a gravid uterus without disrupting the pregnancy or jeopardizing a mother's health or reproductive potential.[4,6] An absorbable stapling device developed for fetal surgery has been applied to routine cesarean sections.[7] More recently, the development of video endoscopic techniques allows fetal manipulation without hysterotomy, greatly extending the indications for fetal surgery.[8] Many innovative techniques developed for fetal surgery—radiotelemetric monitoring of the fetal electrocardiogram and uterine contractions, for instance—may prove useful in managing other high-risk pregnancies.[9] Preterm labor has limited success in fetal surgery much like rejection has limited success in transplantation. An intense effort to solve the vexing problem of preterm labor after hysterotomy for fetal surgery has yielded new insight into the role of nitric oxide in myometrial contractions and a promising new approach to the broader problem of preterm labor using nitric oxide donors.[10,11]

Research expanded on fetal surgery has yielded advances in understanding fetal biology with implications beyond fetal therapy. The observation that a fetus heals surgical incisions without scar has provided new insights into the natural history of wound healing and stimulated efforts to mimic the fetal process postnatally.[12,13]* Fetal tissue appears biologically and immunologically superior for transplantation and for gene therapy, and fetal immune tolerance may allow a wide variety of inherited nonsurgical diseases to be cured by fetal hematopoietic stem cell transplantation.[14-17]

*See also H. P. Lorenz, MD, and N. S. Adzick, MD, "Scarless Skin Wound Repair in the Fetus," on pages 350-355.

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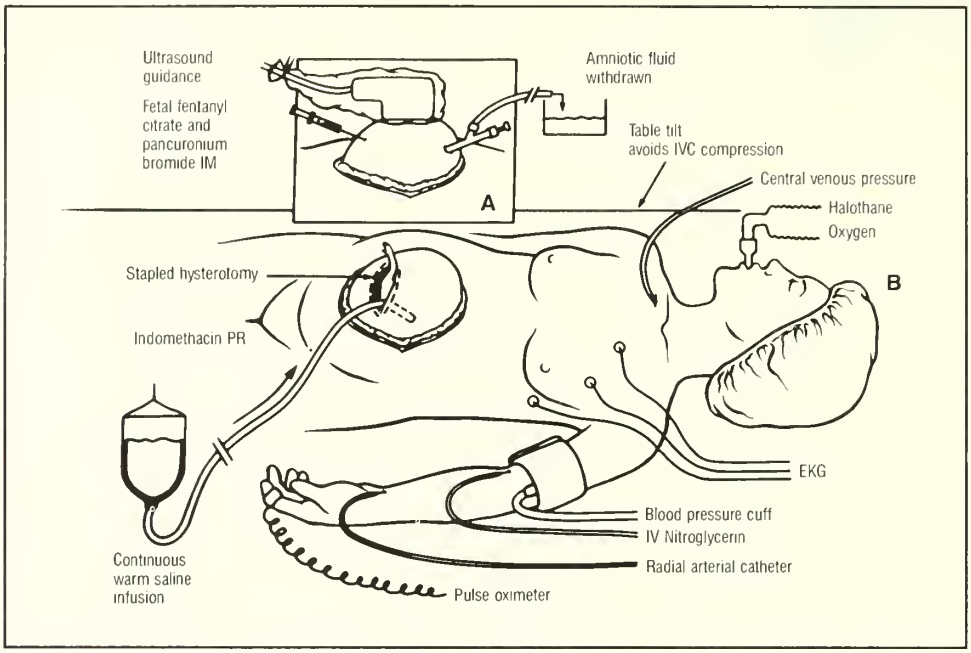

Figure 1.—The diagram shows the technical aspects of fetal surgery. With the maternal adbomen open, ultrasonography is used to localize the placenta and draw a fetal blood specimen before some amniotic fluid is withdrawn. The uterus is opened away from the placenta, and only the pertinent fetal anatomy is exposed. Maternal monitoring is shown; the fetus is monitored by radiotelemeter (adapted from Longaker et al[4]). EKG = electrocardiogram, IM = intramuscularly, IV = intravenous, IVC = inferior vena cava, PR = per rectum

Maternal-Fetal Management

The focus of fetal surgery is not the fetus but the maternal-fetal unit, and successful intervention required a new approach to perinatal care. Maternal safety remains paramount, and the best perioperative management of the maternal-fetal unit requires continuous monitoring of mother and fetus in an intensive care setting (Figure 1). Maternal arterial blood pressure, central venous pressure, urine output, and transcutaneous oxygen saturation are continuously displayed, and blood gas and cardiac output measurements and echocardiograms are done as needed. Monitoring of the fetal condition by intermittent Doppler (for the fetal heart rate) and sonography or echocardiography has been greatly improved by the development of an implanted telemeter that continuously transmits the fetal electrocardiographic results.[9,18] Continuous access to fetal blood through an indwelling catheter may replace intermittent sampling by percutaneous umbilical blood sampling.[19] Uterine contractions, which affect both mother and fetus, can be monitored by external tocodynamometer and palpation, but continuous transmission of the intrauterine pressure by an implanted fetal radiotelemeter has greatly improved the monitoring of preterm labor.[9,10]

Managing preterm labor has proved the Achilles' heel of fetal surgery. The regimen of preoperatively administering indomethacin, intraoperatively administering deep halogenated inhalation anesthesia, and administering indomethacin, magnesium sulfate, and β-mimetics postoperatively, which was worked out in monkeys,[20,21] has proved inadequate for extensive procedures in humans. The depth of anesthesia necessary to achieve intraoperative uterine relaxation can produce fetal and maternal myocardial depression and affect placental perfusion.[22] Indomethacin can constrict the fetal ductus arteriosus, producing tricuspid regurgitation and right-sided heart failure. The combination of magnesium sulfate and β-mimetics can produce maternal pulmonary edema, and fluid restriction to avoid this complication may compromise maternal-placental-fetal circulation and contribute to a recalcitrant preterm labor.[23] The search for a more effective and less toxic tocolytic regimen led to the finding that in rhesus monkeys, exogenous nitric oxide can ablate preterm labor induced by hysterotomy.[10] Demonstrating that exogenous nitric oxide relaxes the laboring uterus raises the intriguing possibility that endogenous nitric oxide mediates uterine relaxation and contraction.[11] Ongoing experimental work in rats, sheep, and monkeys is consistent with this hypothesis, suggesting that the pharmacologic manipulation of nitric oxide may provide an effective treatment of preterm labor. We are pursuing the use of nitric oxide donor drugs for both intraoperative and postoperative tocolysis, hoping that this new approach will help break down this last barrier to successful fetal surgery.

The technical aspects of the surgical procedure have evolved over 15 years of experimental and clinical work.[2,24] The uterus is exposed through a low transverse abdominal incision. Sterile intraoperative sonography is used to delineate the fetal position and placental location. Amniotic fluid is aspirated through a trocar passed under sonographic guidance, and the uterus is opened with a

specially developed absorbable Lactomer stapler that is fast, hemostatic, and seals the membranes to the myometrium.[25] Specially designed, gentle, reverse-biting compression clamps are placed around the incision, and the fetus and uterus are continually bathed in a warm saline solution.

The appropriate fetal part is exposed, and a miniaturized pulse oximeter is wrapped around the fetal palm. A radiotelemetric monitor is implanted subcutaneously and transmits the fetal heart rate, temperature, and intrauterine pressure both intraoperatively and postoperatively (Figure 2).[9] After the defect is repaired, the fetus is returned to the uterus, the staples are removed from the uterine edge, and the hysterotomy sutured closed in layers with fibrin glue to seal the membranes. Warm Ringer's lactate solution replenishes the amniotic fluid volume. The maternal skin is closed with subcuticular sutures so that monitoring devices can be placed on the maternal abdomen postoperatively.

After the patient emerges from anesthesia, the monitoring of maternal hemodynamics, fetal condition, and uterine contractions continues in the fetal intensive care

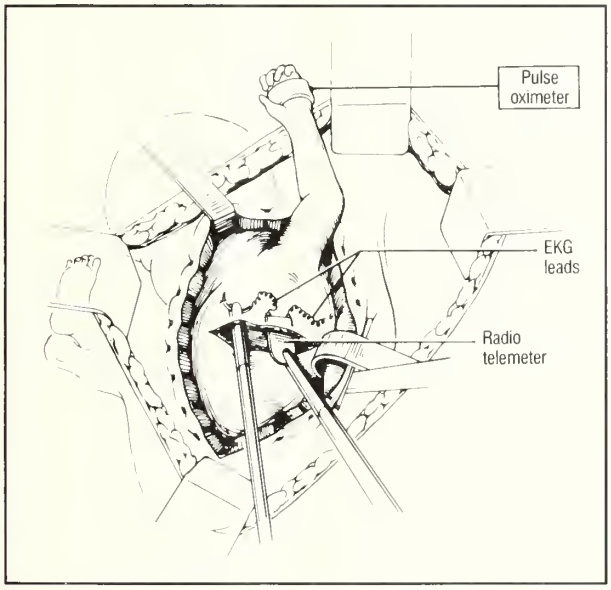

Figure 2.—A radiotelemeter allows the continuous intraoperative and postoperative monitoring of fetal electrocardiogram (EKG) and heart rate. More recently, the transduction of intra-amniotic pressure has also been used for the continuous monitoring of labor (from Harrison and Adzick[24]).

unit. Patient-controlled analgesia or continuous epidural analgesics, or both, ease maternal stress and aid tocolysis. When labor is controlled and the fetus is stable—usually after several days—the patient is transferred to the obstetric ward where radiotelemetric monitoring continues until discharge, usually after a week. Outpatient monitoring and tocolysis continue, and fetal sonograms are done at least weekly. Cesarean section is done when membranes rupture or labor cannot be controlled, usually before 36 weeks.

The learning curve in fetal surgery remains steep. Our group and others continue to develop and test techniques in animals and to then apply them clinically, thus improving maternal and fetal anesthesia, hysterotomy, fetal exposure, fetal monitoring, uterine monitoring, and fetal resuscitation. Many challenges remain, including the need for reliable long-term fetal intravascular access for blood sampling and treatment, noninvasive maternal-fetal hemodynamic assessment, less invasive methods of intervention, including videoscopic surgery, and, most important, the detection and effective treatment of preterm labor.

Risks and Benefits

Fetal therapy raises complex issues. For a fetus, the risk of the procedure is weighed against the benefit of correcting a fatal or debilitating defect. The risks and benefits for a mother are more difficult to assess. Most fetal malformations do not directly threaten the mother's health, yet she must bear some risk and discomfort from the procedure. She may choose to accept the risk to aid her unborn fetus and to alleviate her own burden in raising a child with a severe malformation.

Open fetal surgery poses obvious risks for both mother and fetus. The risk of hysterotomy and open fetal surgery is unknown but potentially formidable. In the 1960s, initial experience with direct surgical exposure of the fetus to catheterize fetal vessels for exchange transfusion was discouraging, and the procedure was quickly abandoned. In the 1980s, after extensive experimental work, newer surgical techniques and improved anesthetic and tocolytic therapy were developed. For example, at the University of California, San Francisco, Fetal Treatment Center, we have performed more than 1,600 procedures in lamb fetuses and 400 procedures in monkey fetuses in the course of developing and refining techniques for maternal-fetal management.[2] This experimental work has made possible the surgical exposure of more than 42 human fetuses for attempted surgical correction of a variety of anatomic defects.

Because open fetal surgery has rarely been attempted elsewhere (one each in Melbourne, Australia; Boston, Massachusetts; Seoul, Korea; Denver, Colorado; and three in Paris, France), the 42 cases at our center provide the best data on maternal outcome. Table 1 summarizes that data through 1992. We have had no maternal deaths and few maternal complications, but our patients have experienced considerable morbidity, primarily related to preterm labor. Five required blood transfusion. The only infectious complications were one case of mild pseudomembranous colitis due to antibiotic therapy, which resolved with a course of oral vancomycin hydrochloride, and one superficial wound infection. Amniotic fluid leaks developed through the hysterotomy site in two patients, requiring reoperation and closure. Amniotic fluid leaks developed from the vagina in three patients, presumably because of fluid dissecting internally from the hysterotomy site to the cervix. All patients had labor after hysterotomy, and the treatment of preterm labor accounted for most of the morbidity; for example, one patient had

mild pulmonary edema from tocolysis. Although not a complication of the operation, two patients have presented with the maternal mirror syndrome (the mother mirrors the fetal hydrops) that progressed after repair of the fetus.

An important aspect of maternal safety is the effect of hysterotomy on a patient's ability to carry subsequent pregnancies. Because the midgestation hysterotomy is classical—not in the lower uterine segment—there is a potential for uterine disruption during labor, so delivery after fetal surgery and all future deliveries should be by cesarean section. In our series, two disruptions occurred in subsequent pregnancies when labor progressed before a cesarean section could be done. Uterine closure and neonatal outcome were excellent in both cases. The ability to carry and deliver subsequent pregnancies does not appear to be jeopardized by fetal surgery; 13 patients have had 14 normal children in subsequent pregnancies, and 3 more are currently pregnant. Seven patients with a previous history of infertility have either not conceived (5) or had early miscarriages (2).

TABLE 1.—*Maternal Outcome With Open Fetal Surgery**

Variable	*Median*	*Range*
Maternal age, yr	26	18-43
Gestational age of fetus, wk	24.2	17-28
Operative time, total, min	127.4	69-182
Operative time, fetal repair, min	34	10-92
Blood loss, ml	455	150-1,400
Interval to delivery, wk	4.1	1-15
Gestational age at delivery, wk	28.4	22-36
Subsequent pregnancy history, No.		
Term cesarean delivery, healthy	14	
Currently pregnant	5	
History of infertility	7	
Not attempted—not desired, too early, and the like	16	

*University of California, San Francisco, Fetal Treatment Center, 42 cases through January 1993.

Anatomic Malformations Amenable to Surgical Correction

The only anatomic malformations that warrant consideration for surgical correction are those that interfere with fetal organ development and that, if alleviated, would allow normal development to proceed (Table 2). At present, only a few life-threatening malformations have been successfully corrected (first five conditions in Table 2). A few others should be successfully treated as their pathophysiology is unraveled (complete heart block, aqueductal stenosis, pulmonary or aortic valve obstruction, and tracheal atresia). When less invasive interventional techniques are developed and proved safe, a few nonlethal anomalies may be considered (myelomeningocele and cleft lip and palate). Fetal stem cell transplantation should open the door to treating a variety of inherited disorders and perhaps to inducing tolerance before birth so organs can be transplanted after birth (stem cell or enzyme defects and organ failure).

Urinary Tract Obstruction

Congenital hydronephrosis due to urethral obstruction is an excellent example of an anatomically simple lesion

TABLE 2.—*Fetal Malformations That Interfere With Development and May Be Surgically Ameliorated Before Birth*

	Effect on Development (Rationale for Treatment)		
Fetal Defects	*Effect*	*Likely Result*	*Treatment*
Life Threatening			
Urinary obstruction (urethral valves)	Hydronephrosis Lung hypoplasia	Renal failure Pulmonary failure	Percutaneous catheter placement, videofetoscopic vesicostomy, open vesicostomy
Cystic adenomatoid malformation	Lung hypoplasia or hydrops	Hydrops and death	Open pulmonary lobectomy
Diaphragmatic hernia	Lung hypoplasia	Pulmonary failure	Open repair; temporary tracheal occlusion*
Sacrococcygeal teratoma	High-output failure	Hydrops and death	Resect tumor; videofetoscopic vascular occlusion*
Twin-twin transfusion syndrome	Vascular steal through placenta	Hydrops and death	Open fetectomy; videofetoscopic division of placenta
Complete heart block	Low-output failure	Hydrops and death	Percutaneous pacemaker; open pacemaker
Aqueductal stenosis	Hydrocephalus	Brain damage	Ventriculoamniotic shunt; open ventriculoperitoneal shunt*
Pulmonary artery or aortic obstruction	Ventricular hypertrophy	Heart failure	Percutaneous valvuloplasty; open valvuloplasty*
Tracheal atresia or stenosis	Overdistension by lung fluid	Hydrops and death	Videofetoscopic tracheostomy*; open tracheostomy*
Not Life Threatening			
Myelomeningocele	Spinal cord damage	Paralysis, neurogenic bladder	Videofetoscopic coverage*; open repair*
Cleft lip and palate	Facial defect	Persistent deformity	Videofetoscopic repair*; open repair*
Metabolic or Cellular			
Stem cell or enzyme defects	Hemoglobinopathy Immunodeficiency Storage disease	Anemia, hydrops Infection Retardation	Fetal stem cell transplant; or gene therapy using fetal stem cells (autologous or allogeneic)*
Predictable organ failure	Hypoplastic heart, kidneys, or lung	Neonatal heart, kidneys, or lung failure	Induce tolerance for postnatal organ transplant using fetal stem cells*

*Not yet attempted in human fetuses.

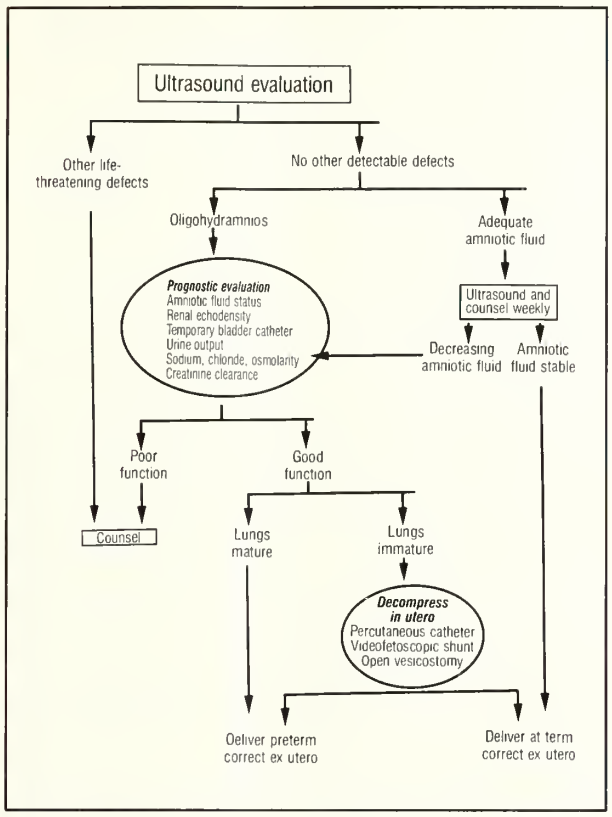

Figure 3.—An algorithm for managing a fetus with bilateral hydronephrosis is shown (adapted from Estes and Harrison[30]).

that has devastating consequences on a developing fetus and that may be prevented by correction before birth.

Fetal urethral obstruction interferes with the development of the fetal kidneys and lungs. Studies in animals have shown that obstruction produces renal dysplasia and pulmonary hypoplasia, and these often-fatal consequences can be ameliorated by decompression before birth.[26,27] The natural history of fetal urinary tract obstruction has now been well documented by serial sonographic follow-up of untreated cases, and selection criteria have been developed based on the ability to predict fetal renal function from fetal urinary electrolyte and β_2-microglobulin levels and the sonographic appearance of the fetal kidneys (Figure 3).[28-30] Although most fetuses do not require intervention, those with bilateral hydronephrosis due to urethral obstruction in whom oligohydramnios develops require either early delivery for postnatal decompression if the lungs are mature or, if the lungs are immature, in utero decompression either by a catheter shunt placed percutaneously under sonographic guidance or by open fetal intervention to create a fetal vesicostomy.[31,32] Fetoscopic placement of an improved mesh stent may solve the technical problems encountered with shunts—malfunction, dislodgement, abdominal wall disruption—and avoid the morbidity of an open surgical procedure.[7] Several hundred fetuses have now been treated. Experience thus far suggests that selection is good enough to avoid intervention in cases that are either too good (do not need it) or too damaged to recover; and that decompression in utero with the restoration of amniotic fluid can prevent the development of fatal pulmonary hypoplasia. It is still not known if decompression affects the course of renal dysplasia or can improve renal functional development.

Cystic Adenomatoid Malformation

Congenital cystic adenomatoid malformation is a benign cystic lung lesion that often presents as a pulmonary mass in infancy or childhood. A subset of cases have a cystic lung mass causing mediastinal shift in utero, however. In some, hydrops and pulmonary hypoplasia develop, and they die in utero—another example of "hidden mortality."[33]

Our experience with more than 30 prenatally diagnosed cases of cystic adenomatoid malformation has confirmed the overriding importance of fetal hydrops as a harbinger of fetal demise. The cause of hydrops appears to be vena caval obstruction or cardiac compression by the huge chest mass as demonstrated in a fetal lamb model.[34] We showed in a lamb model that in utero pulmonary resection is feasible and that compensatory growth of the opposite lung occurs.[35] We then developed an algorithm for the management of this condition (Figure 4).[36]

For severe cases in which hydrops develops before 26 weeks, in utero lobectomy has proved successful.[37,38] Experience with attempted thoracentesis (4 cases) or the placement of thoracoamniotic shunts (3 cases) in fetuses with macrocystic adenomatoid malformation and associated hydrops resulted in a rapid reaccumulation of cyst fluid or inadequate decompression to resolve the hydrops. Subsequently, eight fetuses have undergone open surgical resection of the involved massively enlarged pulmonary lobe. Five of these had a rapid resolution of hydrops, impressive in utero growth of both lungs, and normal postnatal growth and development with a follow-up of 3 to 36 months. The surgical resection of cystic adenomatoid

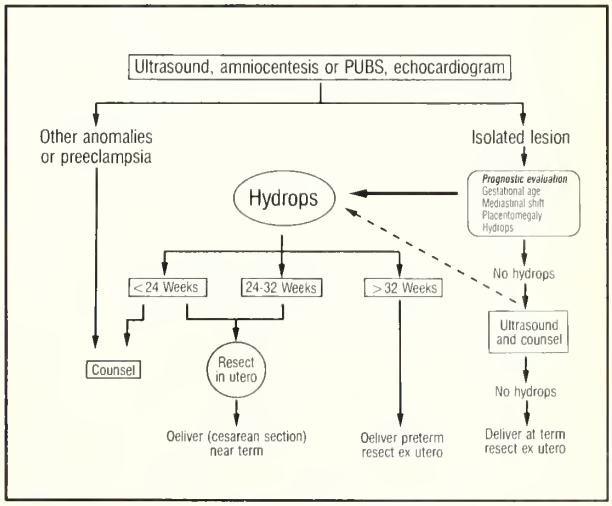

Figure 4.—An algorithm for managing the fetus with cystic adenomatoid malformation of the lung is shown (adapted from Adzick et al[36]). PUBS = percutaneous umbilical blood sampling

malformation in a fetus with hydrops is relatively simple and remarkably successful.

Diaphragmatic Hernia

Congenital diaphragmatic hernia is an anatomically simple defect that is correctable after birth by removing the herniated viscera from the chest and closing the diaphragm. Although less severely affected babies survive with modern postnatal surgical care including extracorporeal membrane oxygenation (ECMO), most babies die despite all intervention because their lungs are underdeveloped.[39,40] Because retrospective estimates of mortality for congenital diaphragmatic hernia vary widely and are flawed by a "hidden mortality"[41] of unknown magnitude, we prospectively studied 52 fetuses with potentially correctable isolated diaphragmatic hernias diagnosed before 24 weeks. The mortality was 60% despite the best postnatal care including ECMO.[5] Babies who die in utero and soon after birth contribute a substantial "hidden mortality." Saving these severely affected babies remains an unsolved problem.

The pulmonary hypoplasia of diaphragmatic hernia is reversible after repair, but weeks or months are required.[42,43] After birth, pulmonary support with ECMO is limited to one or two weeks and cannot save severely affected babies. We have shown experimentally that repair before birth—when the lungs can grow while the fetus remains on "placental ECMO" therapy—is physiologically sound and technically feasible.[44] Repair in utero has proved to be a formidable challenge, however, particularly when the left lobe of the liver is incarcerated in the chest, because reduction of the liver compromises the umbilical blood flow.[45,46]

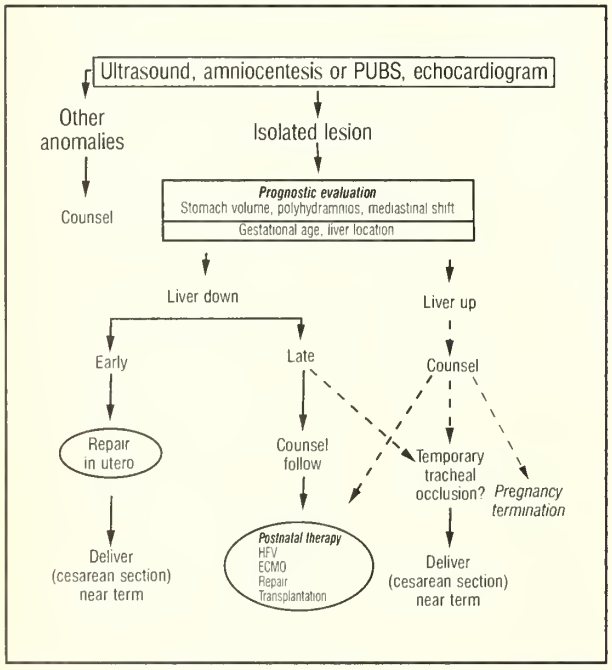

Figure 5.—An algorithm for managing a fetus with diaphragmatic hernia is shown. Fetal surgical repair is being compared with postnatal repair in a National Institutes of Health-funded trial. Temporary tracheal occlusion is a promising experimental approach (see text). ECMO = extracorporeal membrane oxygenation, HFV = high frequency ventilation

The problem of the accurate assessment of the extent of liver herniation has finally yielded to careful evaluation of the umbilical vein or ductus venosus by color Doppler imaging. Fetuses with the vessels above the level of the diaphragm cannot be treated with current techniques and can be excluded. Lesser degrees of herniation can be corrected by reducing the liver, or, if reduction kinks the umbilical circulation, by removing the segment of liver once the position of the ductus venosus is delineated by Doppler ultrasound imaging (J. M. Estes, A. W. Flake, N. S. Adzick, et al: "A Novel Technique for In Utero Liver Resection and an Analysis of Fetal Liver Regeneration," unpublished manuscript, October 1992).[47]

The many technical problems associated with this difficult repair led to the development of the "congenital diaphragmatic hernia two-step," a carefully orchestrated approach that allows the reduction of viscera, the reduction or amputation of the incarcerated liver, reconstruction of the diaphragm, and enlargement of the abdomen to accept the returned viscera.[48]

We have developed an algorithm for managing fetal diaphragmatic hernia (Figure 5). Fetuses with herniation late in gestation, particularly those who do not have a dilated stomach in the chest, have a reasonable outlook and can be delivered near term at a tertiary center. Conversely, fetuses with early herniation, a severe mediastinal shift, and a dilated intrathoracic stomach (the outlet obstruction produces polyhydramnios and gastric dilation) have a poor outlook. If severe liver herniation does not exclude repair, some of these fetuses may be saved by repair in utero.

Although repair before birth appears physiologically sound and technically feasible, it should not be widely applied until efficacy, safety, and cost-effectiveness are documented in a proper prospective trial. After extensive review, the National Institutes of Health has agreed to fund such a trial.

For fetuses deemed untreatable because of liver herniation, we are developing a different approach to improving fetal lung development. In lamb fetuses, impeding the normal egress of fetal lung fluid by controlled tracheal obstruction enlarges the hypoplastic lungs and pushes the viscera back into the abdomen.[49,50] This new procedure, which we call PLUG (*p*lug the *l*ung *u*ntil it *g*rows), may prove useful when total correction in utero is not possible.

Sacrococcygeal Teratoma

Most neonates with sacrococcygeal teratoma survive, and malignant invasion is unusual. The outcome for those with this disorder diagnosed prenatally (by sonogram or elevated α-fetoprotein level) is less favorable, and there is a subset of fetuses with large tumors in whom hydrops from high-output failure develops due to extremely high blood flow through the tumor, essentially a vascular steal.[51,52] Almost all fetuses with sacrococcygeal teratoma in whom hydrops, placentomegaly, or both, develops die

in utero or at birth. Those fetuses may be saved by interrupting the vascular steal.[53]

The excision of a fetal sacrococcygeal teratoma has led to the resolution of fetal hydrops, but it must be done before placentomegaly and the maternal mirror syndrome become irreversible.[54,55] In the future, it may be possible to occlude the tumor vessels by either sonographically guided or fetoscopic techniques.

Twin-Twin Transfusion Syndrome

In some twin pregnancies, abnormal chorionic blood vessels in the placenta connect the circulation of the two fetuses. These placental abnormalities are associated with perinatal mortality as high as 75% for twin-twin transfusion syndrome (anatomically normal twins) and for acardiac-acephalus syndrome (the larger anatomically normal "pump" twin supplies the acardiac "perfused" twin through chorioangiopagus placental anastomoses).[56] Some cases can be managed by serial amniocentesis.[57] In theory, the result can be improved by severing the abnormal placental vascular connection. This has been accomplished by occluding the umbilical circulation percutaneously,[58] by dividing the abnormal placental vessels endoscopically,[59] and by removing the abnormal fetus by hysterotomy.[60] The best approach has not yet been determined.

Heart Block

Fetuses with structurally normal hearts in whom complete heart block associated with maternal collagen-vascular disease develops may have hydrops and die in utero if the ventricular rate falls below 50 beats per minute.[61] If low-output failure cannot be reversed by increasing the heart rate with β-agonists, a pacemaker will be required to save these fetuses (J. M. Estes, N. H. Silverman, G. S. Van Hare, et al: "In Utero Placement of an Epicardial Pacemaker for the Treatment of Congenital Complete Heart Block," unpublished manuscript, December 1992). We have studied the abnormal function of fetal heart block and developed pacing techniques in lamb fetuses.[62] Attempted placement of a pacemaker in a 22-week fetus was unsuccessful because the heart was irreversibly damaged by more than six weeks of failure, so earlier intervention will be necessary.

Aqueductal Stenosis

Another obstructive lesion with severe developmental consequences is obstructive hydrocephalus due to stenosis of the aqueduct of Sylvius. Obstruction to the flow of cerebrospinal fluid produces back pressure that dilates the ventricles, compresses the developing brain, and eventually compromises neurologic function. For severe cases with progression in utero, decompressing the ventricles may ameliorate the adverse effects on the developing brain.[63] Percutaneously placed ventriculoamniotic shunts have not improved the outcome, however,[31] and a moratorium on these procedures is being observed. The natural history of fetal ventriculomegaly needs to be clarified and proper selection criteria developed.[64] The abnormality of obstructive hydrocephalus and its relief must be better defined in experimental models,[65] and fetal shunting techniques as effective as postnatal ventriculoperitoneal shunting must be developed.

Pulmonary or Aortic Valve Obstruction

A few simple structural cardiac defects that interfere with development may benefit from prenatal correction. For example, if obstruction to blood flow across the pulmonary or aortic valve interferes with development of the ventricles or the pulmonary or systemic vasculature, relief of the anatomic obstruction may allow normal development with improved results. Although this abnormality remains to be proved experimentally, aortic stenosis has been dilated by a balloon catheter placed percutaneously,[66] and several centers are developing experimental techniques to correct fetal heart defects.[67]

Tracheal Atresia or Stenosis

Fetuses with congenital high-airway obstruction syndrome have large echogenic lungs due to overdistention by fetal lung fluid. Fetal lung fluid is continuously produced and exported through the larynx and normally provides a distending force that promotes lung growth. With airway obstruction, the lungs overdistend, the diaphragms invert, and often hydrops develops and the fetus dies, a sequence that theoretically should be reversed by decompressing the obstructed trachea (fetal tracheostomy).[68]

Myelomeningocele

Myelomeningocele is becoming less common because it can be detected early in gestation by α-fetoprotein screening and sonography and may be prevented by vitamin supplementation. There is some evidence that neurologic impairment is due to exposure of the spinal cord in utero (M. A. Jordan, C. A. Bittner, K. J. Blakemore, D. S. Heffez, G. M. Hutchins, "The Relationship of the Spinal Cord, Meninges, and Skin in Meningocele, Meningomyelocele, Iniencephaly, and Diastematomyelia," unpublished manuscript), so it may be possible to ameliorate the disabling sequelae by repairing the anatomic defect in utero. We are pursuing this hypothesis experimentally and developing minimally invasive endoscopic techniques for repair. Clinical application for this nonfatal defect is not yet justified.

Cleft Lip and Palate

The observation that fetal wounds heal without scar formation has stimulated interest in the possibility of correcting cleft lip and palate in utero to avoid scarring, midfacial growth restriction, and secondary nasal deformity.[69,70] By the same token, correcting some skull anomalies like craniosynostosis may prevent the development of craniofacial deformities.[71] The theoretical benefits of repair of these nonfatal defects before birth are unproved and do not justify the risks of intervention, however.[72] Further experimental work and the development of less invasive fetoscopic approaches will be necessary before clinical application.

Inherited Defects Correctable by Fetal Stem Cell Transplantation

A wide variety of inherited defects that can now be diagnosed early in gestation, such as hemoglobinopathies and immunodeficiencies, are treated after birth by bone marrow transplantation. But postnatal treatment is limited by donor availability, graft rejection, graft-versus-host disease, and, before the transplant, patient deterioration, which often starts in utero.[73,74] The transplantation of fetal hematopoietic stem cells into a preimmune fetus early in gestation may circumvent all these difficulties.[75] A fetus in early gestation (<16 weeks) is an ideal recipient because it will not reject the transplanted cells, which obviates the need for immunosuppression. In addition, the bone marrow is primed to receive stem cells migratory from the fetal liver, so marrow ablation is not necessary. Also, if donor cells are from a similarly preimmune fetus, graft-versus-host disease does not occur. Thus, hematopoietic chimerism can be established without the need for ablation or immunosuppression. The possibility of creating hematopoietic chimerism was first successfully suggested by Owen's "experiment of nature" in dizygotic cattle twins with cross-circulation.[76] We have confirmed this observation by transplanting fetal hematopoietic stem cells into early-gestation sheep[14] and monkeys[15] and demonstrated long-lasting hematopoietic chimerism of all cell lines without rejection, graft-versus-host disease, or the need for immunosuppression.

Clinical experience with fetal stem cell transplantation is limited, in part because of the restriction on using fetal tissue and the lack of funding for this work. In the few cases attempted, low levels of donor engraftment (relative to recipient's) after fetal intraperitoneal administration have limited the clinical efficacy.[77] Improved fetal vascular access may increase engraftment by allowing repeated injections and sampling.[19]

Predictable Neonatal Organ Failure

The induction of specific immune tolerance by transplanting hematopoietic stem cells in utero may allow organ replacement after birth without rejection or the need for immunosuppression. Several diseases that can be diagnosed prenatally result in predictable neonatal organ failure that could theoretically be cured by transplantation. But organ transplantation in neonates is severely limited by organ shortage, technical considerations, and the need for life-long immunosuppression. A possible solution is to induce immunotolerance by in utero transplantation of allogeneic or xenogeneic hematopoietic stem cells.[78] For a fetus that needs a kidney, lung, or bowel, T cell-depleted hematopoietic stem cells from a relative could be used to prepare for a living-related transplant after birth. For a fetus that needs a heart or liver, xenogeneic stem cells could be used to prepare for a xenotransplant after birth. Although promising, a great deal of experimental work is necessary before clinical application is attempted.

Videofetoscopic Surgery

Although diagnostic visualization of the fetus through small "needlescopes" is not new, recent advances in minimally invasive videoendoscopic surgery now make it possible to do major fetal surgery through small puncture sites in the uterus, thus avoiding the morbidity of a uterine incision—preterm labor, bleeding, potential for later rupture.[7] Diseases possibly treatable by videofetoscopic techniques are noted in Table 2. In addition, we have developed videofetoscopic techniques in fetal animal models to decompress fetal fluid collections (obstructed bladder, cysts) using an expandable wire stent[7]; create and repair cleft lip and palate early enough in gestation to take advantage of scarless fetal healing; and achieve long-term fetal vascular access by inserting catheters in extra-amniotic chorionic vessels on the surface of the placenta.[19] The catheter exits from the uterus without transversing the amniotic space and is connected to a subcutaneous port to lessen the risk of infection. Safe ongoing vascular access will open the door to a variety of fetal therapies including hematopoietic stem cell transplantation and gene therapy.

Several technical problems require experimental resolution before clinical application is attempted:

- The advantages and disadvantages of gas environment (better visualization and risk of air embolism) or a liquid environment (better fetal hemostasis and poor visualization) must be evaluated.
- The possibility of fetal eye damage from bright light or lasers must be studied.
- Techniques for uterine port placement must be bloodless and secure the membranes to the myometrium to prevent leak or dissection.
- Instruments must be miniaturized.

We are currently developing these videofetoscopic techniques in fetal lambs and monkeys and anticipating many exciting clinical applications.

Conclusion

The great promise of fetal therapy is that for some diseases the earliest possible intervention will produce the best possible result. It is preventive therapy in its best sense. The promise of cost-effective, preventive fetal therapy can be subverted by misguided clinical applications, such as a complex in utero procedure that "saves" an otherwise doomed fetus that requires neonatal or lifelong intensive and expensive care. Enthusiasm for fetal intervention must be tempered by respect for the interests of the mother and her family, by careful study of the disease in fetal animals and untreated human fetuses, and by a willingness to abandon therapy that does not prove effective and cost-effective in properly controlled trials.

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Scarless Skin Wound Repair in the Fetus

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The ability of a fetus to heal without scar formation depends on its gestational age at the time of injury and the size of the wound defect. In general, linear incisions heal without scar until late in gestation whereas excisional wounds heal with scar at an earlier gestational age. The profiles of fetal proteoglycans, collagens, and growth factors are different from those in adult wounds. The less-differentiated state of fetal skin is probably an important characteristic responsible for scarless repair. There is minimal inflammation in fetal wounds. Fetal wounds are characterized by high levels of hyaluronic acid and its stimulator(s) with more rapid, highly organized collagen deposition. The roles of peptide growth factors such as transforming growth factor-β and basic fibroblast growth factor are less prominent in fetal than in adult wound healing. Platelet-derived growth factor has been detected in scarless fetal skin wounds, but its role is unknown. An understanding of scarless tissue repair has possible clinical application in the modulation of adult fibrotic diseases and abnormal scar-forming conditions.

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Wounds in fetuses heal rapidly and generally without scar formation until late in gestation.[1] Relative to that in adults, fetal wound repair is characterized by more rapid epithelialization, fibroblast migration, extracellular matrix (ECM) deposition, and the ultimate restoration of normal tissue architecture. Major differences between fetal and adult wound healing are summarized in Table 1. This unique phenomenon of fetal skin wounds healing with a regeneration of normal tissue structure has stimulated research interest in the process of fetal wound healing. An understanding of this phenomenon has clinical implications in possibly modulating adult fibrotic diseases and abnormal scar-forming conditions such as burn contractures, keloids, strictures, and intra-abdominal adhesions.

Fetal Skin

The less-developed state of fetal skin at the time of wounding may be important for scar-free tissue repair. The human fetal epidermis begins with two cell layers, the basal cell layer and the periderm, at about 4 weeks' gestation. The periderm is the outermost single-cell layer of the fetal skin. Its cells have microvilli and blebs projecting off the surface of the skin into the amniotic fluid. Although the function of the periderm has not been determined, a secretive or absorptive process has been hypothesized.[2] As development continues, an intermediate epidermal cell layer develops. Keratinization begins at 9 to 16 weeks' gestation. During this period, primordial hair follicles and sebaceous glands become apparent. By 24 weeks' gestation, the epidermis has completed keratinization and stratifies into adult morphologic layers.[3]

The dermis, which is the location of scar in adult wounds, is similarly undergoing morphologic and biochemical changes. Early in gestation, the fetal dermis is thin and cellular, owing to the paucity of ECM. As development progresses, dermal collagen is deposited and sulfated glycosaminoglycans replace nonsulfated gly-

TABLE 1.—*Comparison of Adult and Fetal Skin Wound Healing Characteristics*

Wound Healing Characteristic	*Adult*	*Fetus*
Scar	Present	Absent
Underlying cell growth and development	Absent	Present
Speed to closure	Slower	Faster
Scab	Present	Absent
Oxygen tension	Greater	Lesser
Fluid environment	Absent	Present
Sterile environment	Absent	Present
Skin temperature	Cooler	Warmer, more uniform
Acute inflammation	Present	Reduced
Matrix deposition	Slower	Faster
Angiogenesis	Greater	Reduced
Epithelialization	Slower	Faster
Keratinization	Present	Immature, periderm

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ABBREVIATIONS USED IN TEXT

ECM = extracellular matrix
FPCL = fibroblast-populated collagen lattice
PVA = polyvinyl alcohol
TGF-β = transforming growth factor-β

cosaminoglycans of which hyaluronic acid is predominant.[4] The rapid growth and the relatively undifferentiated state of fetal skin set the stage for the unique response of fetal skin to injury.

Fetal Environment

Several differences that exist between the fetal and adult environments may affect wound repair. Fetal skin wounds are continuously bathed in warm, sterile amniotic fluid that is rich in growth factors. Fibronectin and hyaluronic acid, which are predominant ECM components in fetal wounds, are also present in amniotic fluid. The continuous presence of amniotic fluid may play a role in the deposition of the scarless wound matrix by providing a growth factor profile not found in the environment of adult skin.

Fetal tissue oxygenation is much less than that of adult tissue. The fetal arterial Po_2 is 20 to 25 mm of mercury, making the fetus much more hypoxemic than the adult.[5] We have measured fetal tissue Po_2 of sheep in midgestation, which is when scarless repair occurs, and found a fetal tissue Po_2 of 16 mm of mercury. Adult wound studies have traditionally emphasized that wound hypoxia may result in impaired leukocyte function, delayed healing, and an increased incidence of infection.[6] These studies in adult animals have shown that supplemental oxygen helps stimulate collagen deposition by adult fibroblasts at the wound edge. The ability of the fetus to heal rapidly and without scar in a relatively hypoxic environment is intriguing and requires further study.

Fetal serum also differs from adult serum. Levels of insulinlike growth factor II and hyaluronic acid stimulating factor have been higher in fetal serum than in adult serum.[7,8] The profile of other growth factors in fetal serum is probably different from that in adult serum, considering that the fetus is continuously growing and developing. Thus, the presence or absence of specific growth factors perfusing the fetal wound may also play a role in scarless repair.

Wounded adult tissue in the fetal environment has been shown not to heal free of scar. We transplanted adult sheep skin onto fetal lambs at 60 days' gestation (term = 145 days), before the fetal immune system has developed sufficiently to reject allografts. The adult grafts were wounded 40 days later (100 days' gestation), at a time when scarless repair occurs in the fetal sheep model. The wounds were analyzed by immunostaining for specific collagen types and were shown to heal with scar formation.[9] Neither an amniotic fluid environment nor perfusion by fetal blood prevented scar formation in wounded adult skin grafts. This suggests that the fetal environment is not crucial for scarless wound healing.

To determine the effect of an adult environment on fetal repair, we transplanted human fetal skin grafts to either a cutaneous or a subcutaneous location on athymic mice. Wounds made in human fetal skin grafts at an identical gestational age (15 to 22 weeks) healed with scar in cutaneous grafts and without scar in the subcutaneous grafts (Figure 1).[10] Immunohistochemical analysis of the wounds with species-specific antibodies against either mouse or human collagen types revealed that the cutaneous graft wounds healed with scar composed of mouse collagens. The subcutaneous graft wounds healed without scar and regenerated with human collagens.[11] Thus, the adult (mouse) fibroblasts deposited collagen with scar formation whereas fetal (human) fibroblasts deposited collagen in a scarless pattern. Scarless repair thus appears to be intrinsic to fetal tissue, and the major fetal cell type responsible for scarless repair may be the fetal fibroblast.

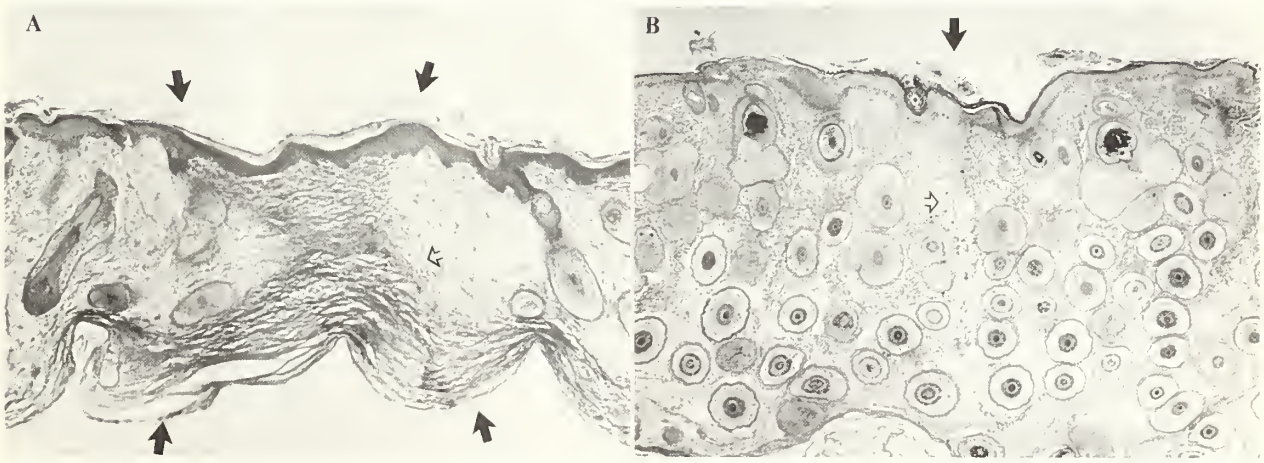

Figure 1.—Human fetal skin at 19 weeks' gestational age was transplanted onto athymic mice, incisionally wounded and tattooed with india ink **(open arrows)** 7 days after transplantation, then harvested 14 days after wounding and stained with Mallory's trichrome. Cutaneous graft **(A)** healed with scar formation **(closed arrows)**. Subcutaneous graft **(B)** healed without scar **(closed arrow)**. The hair follicle and collagen patterns are unchanged from the surrounding unwounded dermis, demonstrating scarless human fetal skin repair (original magnification × 50) (from Lorenz et al[10]).

The ability of fetal skin to heal without scar in an adult environment gives hope that adult skin can be modulated to heal without scar.

Fetal Inflammatory Cells

Although inflammation is an integral component of adult wound repair, evidence is mounting that it plays a much less prominent role in fetal wound healing. The fetal immune system is functionally immature relative to that in adults. Immunohistochemical studies in both fetal lamb[12] and mouse[13] have shown an absence of immunoglobulin deposition in fetal wounds. Fetal polymorphonuclear leukocytes are conspicuously absent in fetal rabbit wounds. Fetal polymorphonuclear leukocytes, however, will migrate into polyvinyl alcohol (PVA) sponges placed subcutaneously into fetal rabbits if the sponges are first implanted and then removed from adult rabbits.[14] This suggests that adult wound chemoattractants can elicit fetal leukocyte migration to the wound site. The lack of acute inflammation in fetal wounds is well documented, but a direct effect on scarless repair remains to be proved.

Wound macrophages coordinate repair in adults, and preliminary studies suggest a similar role in fetuses. Macrophages have been shown to be present in abundance in fetal rabbit wounds by enzyme histochemistry,[15] suggesting site-specific recruitment. Macrophages from adult wounds express many growth factors, and fetal wound macrophages also express growth factor transcripts.[16] In addition, adult wound macrophages are intimately involved in matrix remodeling because these cells express metalloproteinases and their inhibitors, thus coordinating ECM turnover. Because fetal skin repair is characterized by the reformation of a normal ECM, a regulatory role for fetal wound macrophages seems likely.

Fetal Extracellular Matrix

The extracellular matrix comprises several varieties of macromolecules that are reformed in a unique way after injury in the fetus: the ECM integrity is reestablished without scar formation. Hyaluronic acid, collagen, elastin, and adhesion glycoproteins are the major components of the matrix. Their synthesis and organization after injury differs between fetal and adult wound healing.

Hyaluronic Acid

Hyaluronic acid is a high-molecular-weight glycosaminoglycan composed of alternating units of glucuronic acid and *N*-acetylglucosamine. Hyaluronic acid is present in high concentrations during embryogenesis and during periods of rapid tissue proliferation and regeneration.[17] It has been shown to inhibit cell differentiation and can create an environment that promotes cell proliferation. It has a large volume of hydration due to its high charge, which facilitates cellular movement by opening up tissue spaces. These properties have led several investigators to study its role in fetal wound repair.

The fetal sheep model permits fetal surgical manipulation in both the second and third trimesters as well as wound analysis several weeks after injury. We have shown that hyaluronic acid levels in both fetal and adult sheep wounds rapidly increase until three days after wounding. These elevated levels persist at least 21 days after wounding in the fetus, whereas they rapidly return to baseline in the adult.[18] This prolonged presence of hyaluronic acid in fetal wounds may provide an environment conducive to scarless repair.

The prolonged presence of hyaluronic acid in fetal wounds may be due to either its increased synthesis or its decreased degradation. Despite its obvious importance in growth and development, little is known regarding the regulation of its synthesis. Several growth factors have been shown to stimulate hyaluronic acid synthesis. A stimulating activity has been described in fetal bovine sera as a 55-kilodalton glycoprotein. Studies by our group have shown that fetal lamb and bovine sera each contain hyaluronic acid stimulating factor, levels of which peak in midgestation.[19]

To investigate the role of this stimulating factor in fetal wound repair, we measured its levels in fetal sera, wound fluid, and amniotic fluid.[20,21] Analysis of wound fluid from wire-mesh cylinders implanted in midgestational fetal lambs showed elevated levels of hyaluronic acid stimulating activity that was absent in adult wound fluid. Thus, increased stimulating activity in fetal wounds may result in a hyaluronic acid-rich ECM promoting rapid cell mobility and proliferation. High levels of hyaluronic acid and its stimulating factor are also present in amniotic fluid, which bathes fetal skin wounds. This provides another mechanism by which the glycosaminoglycan is made available at the skin wound site.

Mammalian hyaluronic acid also has associated binding proteins that have been implicated in its biologic activity. By comparing purified hyaluronic acid extracts from bacteria that have much less associated binding proteins and human umbilical cord extracts, Burd and colleagues demonstrated that human hyaluronic acid-protein extracts had greater biologic activity: epidermal cell proliferation was increased in explant cultures, and fetal sheep skin explant dermal wound repair was improved.[22] These results suggest that the tightly associated binding proteins confer on hyaluronic acid some of its biologic activity. Their in vivo function in fetal repair remains to be determined.

As more studies are completed, hyaluronic acid becomes ever more implicated in fetal wound healing. Its stimulating activity is present in fetal wounds for a prolonged period, and hyaluronic acid is deposited quickly and persists throughout the period of repair. This mechanism is not present in the adult wound in which the stimulating factor is absent, hyaluronic acid is deposited briefly with fibrin and the platelet plug, it is removed by hyaluronidase, and then this provisional matrix is replaced by collagen and sulfated glycosaminoglycans. The prolonged hyaluronic acid-rich ECM in fetal wounds provides an environment that fosters cell motility and proliferation, which may contribute to scarless repair.

Collagen

The deposition of collagen in fetal wounds is in a highly organized pattern that is indistinguishable from unwounded fetal dermis. The regulation of collagen synthesis and fibrillogenesis is arguably the single most important mechanism underlying scarless repair and remains to be elucidated. Collagen is rapidly deposited in fetal wounds. Whitby and Ferguson, by performing immunohistochemical studies using antibodies to collagen types I, III, IV, and VI, showed that the speed of collagen deposition in mouse lip wounds is inversely related to age (fetal > newborn > adult).[13] In both fetal lambs and fetal rhesus monkeys, a transition from scarless fetal skin repair to healing with collagen scar formation in the middle of the third trimester has been demonstrated.[21,23] This transition shows that there is a spectrum to fetal repair, suggesting that as the fetus differentiates it develops an adult-like wound repair response before birth. A unique "transition" wound during the early third trimester has been described in fetal rhesus monkeys: the wound heals without hair follicles or sweat glands but with a normal reticular collagen pattern.

Quantitative analysis of fetal wound collagen has been done by various methods and in many animal models. There is a similar ratio of type I and III collagen content in fetal rat wounds and unwounded dermis, in which collagen type III is present in greater proportion than in adults. To study collagen content and wound-breaking strength, Burd and associates implanted PVA sponges into 75- and 100-day gestation fetal lambs and nonpregnant adult sheep.[24] Before implantation, the PVA sponges were bisected and the halves stapled together to study wound-breaking strength. Interestingly, the hydroxyproline content was greater in the fetal wounds, but the breaking strength was comparable in the two groups. Recent studies investigating fetal rabbit skin-bursting strength suggest that fetal wounds regain tensile strength more rapidly than adult wounds when compared with normal fetal and adult skin, respectively.[25] The mechanisms underlying this phenomenon have yet to be determined but probably relate to collagen fibrillogenesis and degrees of collagen cross-linking.

In vitro fetal fibroblast studies suggest that these cells are more proficient at collagen production than are adult fibroblasts. The relative collagen synthesis of first- and second-passage fetal rabbit fibroblasts is greater than in adults. Though both fetal and adult fibroblast collagen production drops during the second passage, the fetal fibroblasts produce more type III and V collagen than do the adult fibroblasts.[26] This is not unexpected as fetal skin has a higher ratio of type III to type I collagen. In human fetal skin, type III collagen comprises 30% to 60% of the total whereas in adults it is 10% to 20% of total dermal collagen.[26] In vitro studies of human fetal skin fibroblasts show that the ratio of type I to type III collagen synthesis parallels the ratio of their corresponding messenger RNAs, which suggests coordinated control at the transcriptional level.[27] The relative abundance of type III collagen in fetal skin, and presumably in fetal wounds, may be an important factor in scarless repair.

Differences in the regulation of overall collagen synthesis have been found between fetal and adult fibroblasts. Prolyl hydroxylase controls an important rate-limiting step in collagen production. Studies comparing early-passage human fetal and adult fibroblasts show that prolyl hydroxylase activity in fetal fibroblasts is much greater until about 20 weeks' gestation, after which it begins to fall toward adult levels.[28] Unlike in the adult, fetal prolyl hydroxylase is regulated by polyadenosine diphosphate-ribose synthetase, an enzyme implicated in cell repair and tumorigenesis. Thus, fetal skin collagen type ratios are different, overall collagen synthesis is increased, and a different enzymatic regulation is used in the fetus compared with adults. By investigating these differences, more insight will be gained into the ability of fetal fibroblasts to form highly organized collagen.

An abundance of collagen laid down in the wound matrix in parallel fibers constitutes scar in postnatal wounds, whereas a more organized, reticular collagen deposition pattern characterizes fetal wound repair. As more data accumulate, the effect of specific matrix components takes on greater importance. A hyaluronic acid-rich matrix present early and persisting throughout the period of fetal repair may provide the environment necessary for the orderly deposition of collagen fibrils. Collagen type III fibrils of a narrow diameter have been shown to be present at times when hyaluronic acid is abundant. Collagen fibril diameters increase in midgestation, concomitantly with decreasing hyaluronic acid content.[29] Topically applied tissue-extracted hyaluronic acid improves matrix organization in adult tympanic membrane perforations and results in less scar formation.[30] These studies suggest that adult wound repair can be modified by the exogenous application of specific ECM components found in large quantities in fetal wounds.

Adhesion Glycoproteins

As cells become mobile during embryogenesis and repair, specific interactions occur between them and the ECM that allow cells to detach and migrate. The matrix provides the scaffolding for cell attachment and migration through various glycoprotein components such as fibronectin and tenascin. Cells bind to these adhesion glycoproteins with integrins. Cell motility direction may be determined by the relative integrin-ligand binding affinities of the various adhesion glycoproteins bound to a particular cell.

Some of the major differences between fetal and adult wound repair are the temporal patterns of adhesion glycoproteins present in the wound, which are seen at the earliest stages of repair. These differences may lead to differences in cell mobility, migration, adhesion, and proliferation. Fibronectin and laminin have been demonstrated in fetal and adult rabbit wounds using indirect immunofluorescence techniques.[31] Fibronectin is deposited earlier in fetal than in adult wounds whereas there are no differences in laminin deposition.

Tenascin is an ECM glycoprotein that inhibits the cell adhesion effect of fibronectin by interfering with the integrin-mediated fibroblast attachment to fibronectin. In addition, the appearance of tenascin in the matrix correlates with the initiation of cell migration. Using immunohistochemical staining techniques for fibronectin, laminin, and tenascin in fetal mice and fetal sheep, Whitby and co-workers found that tenascin was deposited rapidly in fetal wounds and that its temporal appearance parallels the rate of wound healing, being most rapid in the fetus and slowest in adults.[32] Tenascin appears before cell migration in each group. Thus, tenascin may initiate cell migration, and its early appearance in the fetal wound may lead to rapid wound closure. The remarkable ability of fetal wounds to rapidly reform dermis and reepithelialize may be due in part to the rapid deposition of specialized ECM glycoproteins during wound repair.

Fetal Wound Contraction

Discrepancies between the various fetal animal models of wound repair exist with regard to the presence or absence of wound contraction. For example, excisional wounds in fetal rabbit skin gape open and increase in size as the fetus grows.[33] Examination of open fetal rabbit wounds for myofibroblasts, the cells thought responsible for wound contraction, by immunohistochemistry and by electron microscopy have failed to show their presence.[34] In contrast, excisional wounds in the fetal lamb show rapid healing with wound contraction. Immunohistochemical staining for α-smooth muscle actin, a marker for myofibroblasts, in excisional wounds of fetal lambs at 100 days' gestation shows myofibroblasts present in the wounds that heal with scar formation.[35] This association of fetal myofibroblasts with wound contraction in fetal wounds that do heal with scar requires further investigation.

An in vitro method, consisting mainly of the fibroblast-populated collagen lattice (FPCL) technique, has been used to further study fetal wound contraction. In this technique, fibroblasts populate and actively contract a collagen lattice. The contractile ability of different fibroblasts on different collagen types and under different media conditions can be assessed quantitatively. Fetal rabbit fibroblasts contract both adult and fetal collagen lattices to a greater extent than do adult fibroblasts. This shows that the absence of fetal rabbit excisional wound contraction is not due to an intrinsic contractile defect in the fetal rabbit fibroblasts. When rabbit amniotic fluid is added to the FPCL medium, contraction is inhibited in a dose-dependent manner, which suggests that rabbit amniotic fluid contains an inhibitor of wound contraction. Similarly, human amniotic fluid has been shown to inhibit both fetal and adult human fibroblast contraction in FPCL.[36] Conversely, sheep amniotic fluid has been shown to stimulate fetal and adult fibroblast contraction in FPCL.[37] Fractionation of amniotic fluid may allow for the identification of such putative factor(s) involved in inhibiting (rabbit and human) or potentiating (sheep) contraction. The treatment of pathologic wound contractures or the enhancement of large open wound contraction may then be possible.

Growth Factors

Polypeptide growth factors are intimately associated with development and adult tissue repair, which implies they have a prominent regulatory function in fetal tissue repair. The application of several growth factors, either alone or in combination, on adult wounds accelerates repair. With the critical effects growth factors have on adult repair, attention has recently turned to the important functions of growth factors in fetal skin repair.

Transforming growth factor-β (TGF-β) induces fibroplasia and increases wound tensile strength in adult wounds, and similar effects have been recorded in fetal wounds. Exogenous TGF-β impregnated in PVA sponges that are then implanted into fetal rabbits results in an acute inflammatory cell infiltrate and fibroplasia.[38] Thus, fetal fibroblasts can respond to TGF-β with increased collagen deposition. Although exogenous TGF-β application results in fetal wound scarring, recent studies show that TGF-β is present in fetal wound fluid and may function as a modulator during scarless fetal repair as the isoforms present are in different ratios between the fetus and adult. These findings suggest that TGF-β functions in a regulatory capacity during scarless fetal repair as well as during adult repair.[16]

Although Whitby and Ferguson used immunohistochemical staining techniques in the fetal mouse model and demonstrated that platelet-derived growth factor polypeptide is present in fetal wounds, the authors could not demonstrate basic fibroblast growth factor or TGF-β in fetal wounds, whereas these growth factors were present in neonatal and adult wounds.[39] The lack of TGF-β staining in the fetal mouse may be due to its actual absence in fetal mouse wounds, its presence in low and nondetectable levels, its presence in different isoforms for which the investigator's antibody was not specific, or its presence in some masked or cryptic form. Investigators in the same laboratory blocked the effects of TGF-β isoforms 1 and 2 with neutralizing antibody in adult rat wounds and found healing with much less scar formation, but with normal wound tensile strength and collagen deposition by 14 days after the wound occurred.[40] This is the first use of knowledge gained from the study of fetal repair applied specifically to enhance adult wound repair.

Wound Healing in Other Fetal Tissues

Most studies have focused on the unique ability of fetal skin to regenerate after injury. Recent work has shown that this does not necessarily extrapolate to other tissue types. To investigate the healing characteristics of mesothelial-lined fetal tissue, we made incisional wounds in the diaphragm muscle of fetal lambs at 100 days' gestation.[41] The wounds were either excluded from or exposed to amniotic fluid to examine the effects of amniotic fluid on the healing process. The fetal diaphragm wounds healed with scarring, independent of amniotic fluid exposure, at a gestational age when skin healed without scar.

The healing of fetal long bone fractures has also been examined in fetal lambs by our group.[42] Both incisional and excisional fetal bone wounds heal rapidly and with

minimal callus formation. Incisional fetal bone wounds appear to heal by endochondral ossification in which no cartilage intermediate is present in the callus, unlike adult long bones that heal by endochondral new bone formation wherein a cartilaginous intermediate is present in the callus. Even more remarkable is that excisional wound lengths of three times the bone diameter, including periosteum, completely healed in the fetus. A defect of that size in adult long bone invariably results in nonunion. Fetal hard tissue repair is only now beginning to be studied and may lead to better postnatal bone repair.

Future Implications

There are multiple mechanistic differences between fetal and adult wound repair that are just beginning to be elucidated and that ultimately result in dramatically different end points: scar-free fetal repair versus scar formation in adults. These differences include the wound environment, the differentiation of wound repair effector cells, the deposition of early and late ECM components, and the modulation of type-specific collagen fibrillogenesis. As we gain understanding of these differences and new knowledge of fetal cell-cell, cell-matrix, and cell-growth factor interactions, the possibility of the modulation of adult wound scar formation may be realized. Although the possibility of in utero surgical procedures to take advantage of the unique fetal scarless repair process and correct craniofacial anomalies exists, the greatest clinical benefit of studying and understanding the biology of fetal repair may be in developing therapeutic strategies to avert postnatal scarring and fibrosis.

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Stem Cell Transplantation

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Modern physicians desire not only to treat but to cure congenital diseases. In a wide variety of diseases, bone marrow transplantation can be the tool of final cure. The limitations and risks of this procedure have motivated researchers to search for an earlier and safer method of treatment. Special features of fetal immune systems make it possible to perform the transplantation during fetal life using fetal hematopoietic stem cells, thus avoiding many of the side effects of bone marrow transplantation in neonatal life. We review the experimental work done with animal models in this field and the human trials that have been published recently.

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Postnatal bone marrow transplantation is one possible choice in the treatment of children with a wide variety of inherited diseases. This procedure became widespread through pioneering work on the function of stem cells and the immune processes of transplantation. Initially, bone marrow transplantation was used as a therapy for diseases affecting various cell lines derived from stem cells, such as severe combined immunodeficiency disease, Wiskott-Aldrich syndrome, and the leukemias. The therapy was later proved effective in metabolic diseases such as Hurler's syndrome. Considerable limitations and risks exist with this form of therapy, however:

- An HLA-compatible donor is not always available.
- The immune response of a recipient's bone marrow must be suppressed using chemotherapy and irradiation.
- Graft-versus-host disease occurs frequently.
- The disease state may have already caused irreversible damage to the newborn.

These problems with postnatal bone marrow transplantation have motivated researchers to look for earlier and safer methods of treatment. The development of prenatal diagnostic procedures and genetic techniques has aided the search and suggested the possibility of prenatal therapy. The characteristics of fetal immunology make stem cell transplantation in utero possible using fetal stem cells, and this procedure promises to reduce the risks and disadvantages of postnatal transplantation procedures. The undeveloped immune state of the fetus eliminates the requirement for HLA compatibility and the need to actively suppress the recipient's immune response. Treating an inherited disease during gestation may offer the opportunity to correct the defect before irreversible damage occurs. The therapeutic promise of prenatal stem cell transplantation has made this procedure the object of intensive study.

Characteristics of Fetal Hematopoiesis and Immune Response

Hematopoietic stem cells originate from the yolk sac during the first few weeks of embryonic development. In the sixth and seventh weeks of human gestation, these multipotent cells migrate to the fetal liver and spleen.[1] The stem cells can differentiate into various hematopoietic and reticuloendothelial cell lineages while continuously renewing themselves. Another migration occurs during the 18th through the 20th weeks of pregnancy, when the stem cells begin to occupy the bone marrow. By the time of delivery, the only organ of hematopoiesis is the bone marrow, except in a few diseases, such as erythroblastosis fetalis, that necessitate the persistence of extramedullar hematopoiesis.

Meanwhile, the fetal immune system continues to mature. During pregnancy, the fetus is at first completely, and later partially, immunoincompetent: The inability to distinguish "self" from "foreign" causes the fetus to be immunotolerant. The placenta protects the fetus from most foreign cells and, by allowing maternal immunoglobulin G antibodies to cross this barrier, provides the fetus with immune protection. Early observations confirm that cells penetrating the placenta are accepted by the fetus and can survive long term.

A naturally occurring chimera in bovine twins due to intrauterine vascular connections was first described by Owen in 1945.[2] A follow-up study of 65 children who received transfusions in utero demonstrated circulating donor leukocytes in 5 of them a year after birth.[3] These incidents are possible because of the late development of

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fetal T lymphocytes, which are responsible for cellular immunity and the rejection of foreign grafts.[4]

Pluripotent stem cells that give rise to T lymphocytes must mature. The first wave of stem cell inflow into the thymus occurs around the eighth week of gestation.[4] Human fetal lymphocytes can proliferate in response to mitogens by the 11th to the 12th week. Postthymic T lymphocytes are capable of causing fatal graft-versus-host disease and are responsible for graft rejection; these are detected in the liver only after the 18th week of gestation.[5] These aspects of early fetal immune development make the early fetus an optimal donor and recipient.

Research in Animals

Since the observation by Lorenz and colleagues in 1951 that the bone marrow of lethally irradiated mice could be reconstituted by donor bone marrow cells,[6] remarkable efforts have been made to explain the mechanism of that therapy and to determine the advantages and risks of stem cell transplantation using various animal models. We review here selected results of studies in animals.

Mouse Models

An early observation with the in utero administration of allogeneic tissues into mouse fetuses led to the concept in 1953 of "actively acquired tolerance." Billingham and associates confirmed, with skin transplantation on the newborns injected in utero, that mice never develop, or develop to only a limited degree, immune reactivity against foreign homologous tissue to which they have been exposed sufficiently early in life.[7] They also observed that acquired tolerance is caused by a failure of the host's immune response and not by an antigenic adaptation of the grafted cells.[7]

The advantage of fetal liver cells as a source of donor stem cells was demonstrated in 1958, when Uphoff observed a reduced risk of graft-versus-host disease using fetal hematopoietic stem cells (HSCs) to reconstitute the bone marrow of lethally irradiated mice.[8] In 1966 the autosomal recessive, anemic WW mouse model was introduced. Stem cells derived from the livers of 15- to 16-day-old fetuses and transplanted into newborns cured normocytic anemia in 6 of 11 newborns.[9] Hemoglobin patterns derived from the donor erythrocytes were detected by cellulose acetate paper electrophoresis.[10] This was the first time that allogeneic fetal HSCs were used to treat a genetic disease.

In 1972 a comparative study using radioactivity incorporation showed that fetal stem cells are capable, on average, of producing larger descendant populations than are stem cells from adult bone marrow.[11] Fleischman and Mintz in 1979 were the first to use the fetus as a *recipient* of fetal HSCs.[12] They reported successful engraftment in the WW mouse model, administering fetal HSCs to the midgestational mouse placenta. A different approach, the intraperitoneal administration of HSCs, was also shown to be effective when colony-forming units were demonstrated in the spleen after fetal liver cell transplantation.[13]

Sheep Model

The first large animal model was created in 1982 by Zanjani and co-workers.[14] They transplanted adult bone marrow into sheep fetuses intravenously by placing a long-term catheter into the fetal femoral artery. This method allowed blood specimens to be obtained even before birth. Successful grafts were observed in 3 of the 5 animals surviving to birth, from 11 transplanted fetuses. The high loss rate may have been related to graft-versus-host disease. In their model, they proved that T-cell depletion of donor adult bone marrow resulted in a substantial decrease in colony formation in vitro and in reduced engraftment in vivo.[15] To avoid graft-versus-host disease, the group used fetal stem cells by the intraperitoneal route, and they had a similar success rate. Three of four fetuses were born with clear evidence of donor cell engraftment as determined by both hemoglobin type and chromosome analysis.[16]

Monkey Model

The animal models discussed earlier helped researchers to understand the development of fetal immunity and the mechanisms of HSC transplantation. Nevertheless, differences between animal and human physiology necessitated the creation of a more similar model. The results of a primate model were published in 1989 and confirmed engraftment in five of five newborn rhesus monkeys that had been transplanted in utero with fetal liver cells.[17] This study showed evidence of donor cells derived from opposite-sex fetuses in erythroid, myeloid, and lymphoid cells in recipient bone marrow.[17] Later, the data from 11 fetuses determined that the most effective time of donor cell administration was between the 60th and 80th days of gestation (term being 165 days in rhesus monkeys). This period is late enough to lower the probability of abortion and early enough to ensure a high probability of engraftment.[14]

Human Cases

Since 1968 when the first cases of bone marrow transplantation in children were reported,[18,19] hematopoietic stem cell transplantation has become a routine procedure in clinical practice. Several long-term follow-up case studies have been published that confirm the efficacy of the procedure. In 1984, Meuwissen and colleagues described the 15-year survival of a patient with Wiskott-Aldrich syndrome[20] with full T-cell, partial B-cell, and no erythroid engraftment who had received an HSC transplant in 1968.[19] With increasing study, however, limitations and risks have become clearer. Many undesirable side effects are associated with the immune status of the donor and recipient. The patients most likely to have a high engraftment rate are children with severe combined immunodeficiency, who cannot reject the donor cells. The risks of rejection and graft-versus-host disease can be reduced by using HLA-identical donors, but these can be identified for only 35% to 50% of patients. In addition, severe graft-versus-host disease may still be seen in 35% to 60% of HLA-matched patients.[21] Efforts to prevent the

disease by in vitro T-cell depletion of the donor bone marrow have reduced but have not solved the problem.

To avoid these immunologic problems while finding an accessible treatment for those children without an HLA-compatible donor, investigators selected another source of stem cells: fetal liver cells.[22,23] The only reported incidence of graft-versus-host disease occurred in a patient who received liver cells from a 16-week-old fetus.[24] This observation reinforces the preference for using cells derived from donor fetuses younger than 14 weeks' gestation.

Another problem is that by the time children are diagnosed and prepared for HSC transplantation, they may already have been damaged by the disease or by recurrent infections, irreversible mental retardation, or interventions like multiple blood transfusions.

In the past few years, approximately a dozen attempts have been made worldwide to perform stem cell transplantation prenatally. The first human in utero transplantation was reported in 1986.[25] The 17-week-old fetus received T-cell–depleted maternal bone marrow. No engraftment of Rh-negative cells was observed. During the pregnancy, several intrauterine transfusions were required. No engraftment was detectable as well in six other cases transplanted in utero with T-cell–depleted parental bone marrow.[26]

The only successful prenatal stem cell transplantations have been reported from France, using fetal stem cells.[27,28] Touraine and co-workers have treated four fetuses. Their first case was a 28-week-old fetus with the bare lymphocyte syndrome; they transplanted fetal HSCs into the umbilical vein.[27] The child was born in 1988 with evidence of engraftment—initially 10% and then 26% of lymphocytes of donor origin—and with absolute clinical reconstitution.[28] They administered fetal stem cells intravascularly in two additional cases (at the 26th and 17th weeks of gestation) and intraperitoneally in one case (at the 12th week). The indications for therapy were immunodeficiency in one case and thalassemia in two other fetuses. The follow-up studies demonstrated evidence of cells or DNA of donor origin in two newborns.[29]

Future Progress

Despite wide-ranging research and clinical work, several questions must be answered before intrauterine fetal stem cell transplantation can become a routine clinical procedure. The optimal age of donor cells is well established: before the 14th week of human gestation, before T cells appear in fetal liver. Less clear is the importance of the recipient's age at the time of fetal transplantation. From a technical point of view, the only possible approach before the 18th to 20th week is the intraperitoneal route. Research is required to determine which is more important to achieving increased engraftment: earlier treatment, using the available space in fetal bone marrow and offering decreased probability of rejection, or intravenous administration offering easier uptake of donor cells. The effectiveness of treatment may depend on the condition of the donor stem cells. New in vitro techniques are being developed to enhance stem cell numbers and effectivity.

Also offering great promise in the prenatal treatment of inherited monogeneic diseases is stem cell-mediated gene therapy.[30] Fetal stem cells derived from liver or from umbilical cord blood[31] and transfected in vitro with the desired copy of the gene in question may correct such diseases after these cells are reinjected into the fetal circulation.

Crucially, ethical considerations must regulate these manipulations, especially in human therapies. This requires the involvement not only of researchers and clinicians, but of philosophers, ethicists, educators, and lawmakers. Most important, it demands the involvement of an educated public.

Conclusions

In the past few decades, the transplantation of hematopoietic stem cells has become an important tool in treating a broad spectrum of hematopoietic and metabolic diseases. The disadvantages of postnatal bone marrow transplantation have motivated researchers and clinicians to create new procedures to overcome these hurdles.

The fetus is a proven optimal donor because:

- No T-cell depletion is required,
- No graft-versus-host disease occurs, and
- A high engraftment rate is seen.

The fetus is an optimal recipient as well because:

- No HLA matching is required,
- No immunosuppression is required,
- The probability of rejection is decreased,
- Space is available in the fetal bone marrow, and
- Early prenatal treatment can cure the condition before irreversible damage has occurred.

In selected cases when the diagnosis can be established early enough in gestation and the disease is life-threatening, intrauterine fetal stem cell transplantation is a feasible treatment of congenital disease in the hope of a long-term cure.

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Cytogenetic Analysis in Prenatal Diagnosis

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Chromosome analysis is the single most frequent test used in laboratory prenatal diagnostic studies. I summarize the current status of the field, including diagnostic problems in the laboratory and the clinical problems associated with communicating unexpected laboratory findings. I explore the effect of molecular genetics on these issues and its possible future effects on the entire practice of prenatal diagnosis as it relates to the risk for chromosome nondisjunction (trisomy). I also discuss the use of cytogenetic analysis in the prenatal diagnosis of certain inherited genetic diseases.

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Chromosome abnormality, represented primarily by numerical change (trisomy resulting from nondisjunction or triploidy due to dispermy), is the single greatest contributor to prenatal morbidity and mortality. About 30% of recognized cases of embryonic and fetal death is due to chromosome abnormality. The incidence in unrecognized pregnancies—those resulting in early fetal demise—may be much higher.[1] As discussed elsewhere in this issue,* an increased risk of nondisjunction associated with either increased maternal age or positive maternal serum screening tests represents the most frequent indication for prenatal diagnosis. Laboratory methods for cell culture of amniotic fluid and chorionic villi, or in exceptional situations, fetal blood specimens, and for preparing "chromosome spreads" from these specimens are well established and have been extensively reviewed.[2] These will be discussed only to the extent that they are relevant to problems of cytogenetic and clinical interpretation. Although most prenatal cytogenetic studies are unambiguous, cytogenetic laboratories routinely put major efforts into discovering and interpreting the relatively rare class of "unexpected" findings including structural chromosome change and mosaicism—the presence of more than one chromosome complement (karyotype) in cell culture. In this review I will focus on the workup and interpretation of such findings. In addition, I will discuss the potential for introducing new methods into routine prenatal diagnosis and the use of cytogenetic methods in the prenatal diagnosis of several inherited genetic diseases (recessive and X-linked).

*See L. P. Shulman, MD, and S. Elias, MD, "Amniocentesis and Chorionic Villus Sampling," on pages 260-268; and N. C. Rose, MD, and M. T. Mennuti, MD, "Maternal Serum Screening for Neural Tube Defects and Fetal Chromosome Abnormalities," on pages 312-317.

Methods

Cell Culture

Culture success rates for both chorionic villus sampling (CVS) and amniocentesis are typically greater than 99%, with exceedingly low laboratory error rates (<<1%). Amniocentesis represents the first established method for fetal cell sampling and continues to provide the most common specimen type processed for prenatal chromosome analysis. Results are typically available in nine days to two weeks. Cell culture for amniotic fluid specimens is performed in either of two ways. In one, cells are randomly allocated before the production of chromosome spreads (flask technique), and in the other, cells are analyzed as components of the original colonies from which they arose (in situ technique). Each colony, in theory, will have been initiated from a single viable cell in the amniotic fluid specimen. As will be discussed, methods for interpreting mosaicism differ somewhat depending on the technique in use.[3,4] Chorionic villus sampling, being a sampling from actively proliferating tissue, affords the possibility of a "direct" chromosome preparation, with results obtained in the laboratory within two days. Because direct CVS preparations have been found to have slightly more false-negative results, particularly with respect to true fetal mosaicism, and because the chromosome structure and resolution of chromosome bands (each chromosome is identified by a highly specific longitudinal "banding" pattern) are often suboptimal, it is the standard of practice that final results are not communicated before cultured CVS specimens are analyzed.[5] The time frame for reporting results from cultured CVS specimens is similar to that for amniocentesis. At prenatal diagnostic centers with the availability of fetal blood

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ABBREVIATIONS USED IN TEXT

CVS = chorionic villus sampling
FISH = fluorescent in situ hybridization

sampling, chromosome analysis of fetal lymphocytes, by methods not fundamentally different from those used for routine postnatal chromosome analysis, allows both a rapid high-resolution chromosome study and the analysis of many independent cells derived directly from fetal tissue. This method, which entails a higher risk to the pregnancy than either amniocentesis or CVS, is used to obtain rapid (2 days) results required for pregnancy or delivery management or to address clinical ambiguities (such as mosaicism) arising from previous prenatal sampling and analysis.[6,7]

Chromosome Identification

The routine method of analysis for all specimen types is typically G banding, based on the effects of a protease (trypsin) and stain (Giemsa) on fixed chromosome preparations. In addition, cytogeneticists have at their disposal a wide array of staining techniques that allow specific questions arising during the analysis of any particular specimen to be resolved. Such questions usually arise in relation to structural chromosome abnormalities or to extreme variation in chromosomal regions known to vary somewhat in the general population. Among these methods is a powerful technique, introduced over the past several years, that allows cytogeneticists to ask specific questions about the origin of any particular chromosome region. The method—fluorescent in situ hybridization (FISH)—is based on the ability, through molecular genetic techniques, to clone—that is, to isolate and amplify—DNA specific either to a unique region of a single chromosome or to an entire chromosome (the latter used for "chromosome painting"). Such DNA is labeled with a molecule that can later be detected through the use of fluorescence microscopy. The labeled DNA, or "probe," is hybridized to a chromosome preparation from the specimen in question. Fluorescent visualization allows the cytogeneticist to determine whether the abnormal (or potentially abnormal) chromosome region is derived from the same region of chromosome (or, for painting, the same chromosome) as was the probe.[8] A limitation of this method is that it must first be determined which probes might include DNA from the region in question. Technologies now being developed but not yet available for routine use in clinical cytogenetics laboratories may overcome that limitation.[9,10]

Interphase Fluorescent In Situ Hybridization

Routine karyotype analysis is done on chromosome preparations from proliferating cells. Cells prepared for such analyses are typically blocked in the metaphase stage of mitosis with a mitotic spindle poison (colchicine) before "harvesting" for chromosome preparations. The chromosomes are present as integral structures throughout the cell cycle, but cannot be visualized in a way useful to the cytogeneticist except at metaphase. The probes used in FISH techniques are not limited to use with metaphase chromosomes. Through the use of the relevant chromosome-specific probes (for chromosomes 13, 18, 21, X, and Y), the indication for most prenatal cytogenetic analysis—increased risk of nondisjunction—can be rapidly addressed in nonproliferating interphase cells from amniotic fluid or chorionic villi.[11,12] As indicated, the standard of practice in prenatal cytogenetics is to accurately address all possible cytogenetic abnormalities in specimens, not just those related to the procedural indication. As such, the obstetrical and genetics communities generally agree that interphase FISH should not be used as a sole procedure for routine prenatal diagnostic studies, as it does not address the possible presence of unexpected chromosome abnormalities. Optimized methods for the screening of fetal cells in maternal circulation* may necessitate further exploration of that issue in the future. The issue of whether interphase FISH should be used as an adjunct to conventional cytogenetics with preliminary results (1 to 2 days) based on the method released to referring physicians is a much more controversial one.[13,14] A high success rate with the technology has been reported by one group (Integrated Genetics) on a series of 4,500 specimens.[15] The results of such studies should not be used as the sole basis for irreversible therapeutic decisions.

Problems of Interpretation

Mosaicism

The detection of mosaicism or suspected mosaicism in prenatal diagnostic specimens raises issues of two types. The first is related to the laboratory interpretation of the findings—that is, Does the finding in culture represent the true status of the amniotic fluid or chorionic villi? The second is related to the clinical importance of the findings: How likely is it that the mosaicism detected in culture is representative of the true status of the fetus? and, What is the prognosis for the fetus after the finding of true mosaicism for the abnormality in question?

Cytogenetic features. There is an extensive literature on the cytogenetic definition of mosaicism in cell culture and on methods to address suspected mosaicism.[3,4,16] The critical issue is whether the cytogenetic finding represents the status of cells present in the sampled tissue or whether it represents an artifact of cell culture (pseudomosaicism). In the flask method of amniotic fluid culture, and in chorionic villi culture, true mosaicism is defined as multiple (at least two) cells with the same abnormal karyotype present in at least two independent vessels. The in situ method for amniotic fluid has the advantage in the interpretation of mosaicism that it can be readily determined whether an abnormal cell line has arisen entirely from a single amniotic fluid colony (pseudomosaicism) or from many

*See J. Chueh, MD, and M. S. Golbus, MD, "Prenatal Diagnosis Using Fetal Cells From the Maternal Circulation," on pages 308-311.

colonies. Because the possibility always exists that a second or third abnormal colony in a single in situ preparation was actually established from a progenitor cell that floated off one original abnormal colony, there is typically an extensive search for evidence of the abnormal line in a completely independent culture (analogous to the flask method). This is particularly the case if the suspected abnormality is of known clinical significance. A large group of practicing cytogeneticists from the northeastern United States has recently published proposed guidelines for laboratories to address these issues using both the flask and in situ methods.[17]

Clinical management. Cytogenetically defined true mosaicism is detected in less than 0.5% of amniotic fluid specimens and in 1% to 2% of CVS specimens. The finding of true mosaicism in amniotic fluid culture often raises a set of difficult issues related to clinical management. Certain mosaic trisomies, in particular that for chromosome number 2, are known to be detected relatively commonly in amniotic fluid culture (and CVS) and to be without clinical consequence. Most chromosomes of the human complement have not been described in either a pure or mosaic trisomy state in the liveborn population, either from consecutive liveborn studies or from persons karyotyped because of clinical indications. The rare finding of these chromosomes as trisomies (autosomal monosomy, except for cases involving chromosomes 21 or 22, is unreported in liveborn or prenatal studies) in amniotic fluid culture will therefore typically be followed up only by noninvasive ultrasonography. Only in cases with high representation of the abnormal cell line, or when ultrasonographic findings are abnormal, is fetal blood sampling recommended as a follow-up procedure. Because discrepancies between amniotic fluid cell and fetal karyotype are rare, high levels of a clinically important abnormal cell line in mosaic state will usually be accepted as indicative of fetal status; counseling in such cases will describe the spectrum of abnormalities associated with the karyotype and inform of available reproductive options. The finding, in amniotic fluid culture, of low-level true autosomal mosaicism for a trisomy of known clinical consequence will usually serve as an indication for fetal blood sampling. Fetal blood for determining the presence of mosaicism has several advantages over amniotic fluid and CVS:

- It is, unlike the other two procedures, a direct sampling of fetal tissue;
- It allows the analysis of many (>>100, if required) metaphase cells; and
- The short-term culture assures that the cells scored are relatively independent of one another.

After normal results on fetal blood sampling, genetic counseling can be optimistic. The confirmation of low-level mosaicism in fetal blood presents a prognostic problem because there is little unbiased information available on the range of clinical effects associated with low levels of mosaicism for autosomal trisomies. Mosaic numerical abnormalities of the sex chromosomes present similar prognostic problems; unbiased prospective data are rare, and the spectrum of abnormalities associated with both the mosaic and nonmosaic states is wide, with the range of mentation (measured, for example, as IQ scores) substantially overlapping the normal range.[18] Counseling from a geneticist well versed in this area is essential for prenatally detected cases of mosaic and nonmosaic sex chromosome anomalies. Prospective studies of liveborn children with prenatally detected 45,X/46,XY mosaicism suggest that most (95%) will have normal external male genitalia but that the incidence of abnormalities of gonadal tissue structure may be increased.[19]

As noted, mosaicism is more common in CVS (both direct and cultured specimens) than in amniotic fluid cultures. This is due to a special feature of the tissue that is sampled (chorion mesenchymal core for cultured specimens and cytotrophoblast for direct) and has been termed confined placental mosaicism.[20] This phenomenon represents mosaicism limited to the extraembryonic membranes and is not detected in fetal tissues; it occurs in 1% to 2% of CVS cultures.[5,21,22] A growing set of data suggests that confined placental mosaicism, while not associated with fetal karyotypic abnormality, may be associated with intrauterine growth retardation and perinatal loss.[23,24] Although information is continuing to be collected in this area, amniocentesis is often recommended as a follow-up procedure after the discovery of CVS mosaicism. If the mosaicism involves a clinically important trisomy, fetal blood sampling may also be recommended. Strong evidence exists, indeed, that placental mosaicism involving a normal cell line along with a cell line trisomic for chromosome 13 or 18 may be an important etiologic factor in the survival to term of some fetuses fully trisomic for chromosome 13 or 18.[25] The normal cell line apparently arises by the loss of a chromosome from an originally trisomic cell line. In about a third of such cases both homologues of either chromosome 13 or 18 will have arisen from one parent, the contribution from the second parent having been lost. This is known as uniparental disomy and has come to be recognized as a factor in human morbidity over the past several years.[26] In at least one reported case, confined placental mosaicism for trisomy 15 (not a viable fetal trisomy) has been followed by the birth of a child affected with the Prader-Willi syndrome—a syndrome known to be associated with maternal uniparental disomy (no paternal contribution) of chromosome 15.[27] In addition, uniparental disomy for chromosome 16 has been presented as a possible cause of the morbidity associated with confined placental mosaicism of chromosome 16.[24] This raises an as-yet-unresolved diagnostic question: Should molecular evidence for uniparental disomy be pursued in cases of confined placental mosaicism involving chromosomes known to cause morbidity when present in the uniparental disomic state?

Prognostic Issues in Cytogenetics

The woman or couple referred for a prenatal diagnosis because of an increased risk of autosomal trisomy can

expect the result to be relatively "straightforward," either normal or trisomic, trisomy for chromosome 21 being, by far, the most commonly detected abnormality. Several areas in which counseling is more complex have been discussed earlier, including mosaicism and sex chromosome abnormality. Several other findings, all of which fall into the category of "unexpected chromosome abnormalities" are discussed further. These include both extra, de novo (noninherited) "marker" chromosomes and de novo apparently balanced structural rearrangements. In both cases, as with mosaic trisomy, the counselor must present a risk associated with the abnormality. These tend to be difficult counseling issues for patients who were expecting either clearly normal or abnormal results.

Marker chromosomes. Marker chromosomes is a term used to describe small accessory chromosomes, typically of unknown origin. Such chromosomes are often present in a mosaic state. A proportion of marker chromosomes are found to be inherited from normal parents and impart no increased risk to the pregnancies. In about 1 of 2,500 prenatal diagnoses, a de novo marker chromosome is discovered.[28] In a proportion of such cases, particularly with the increased availability of molecular probes, the chromosome can be defined as one known to be consistently associated with a clinical syndrome.[29,30] For markers that appear to have a substantial amount of chromosome material staining as "euchromatin" (gene-encoding regions), the prognosis is typically poor.[31] For most markers, however, geneticists must rely on empirical risk figures derived from the limited number of cases in which markers were ascertained prenatally, the pregnancy maintained, and clinical follow-up achieved.[28] The risk for some abnormality in a newborn tends to fall between 10% and 15%, but has wide confidence limits. The ability to define more precisely the chromosomal makeup of marker chromosomes may ease this difficult counseling issue in the future.[32]

De novo apparently balanced rearrangements. Balanced chromosome rearrangements are a class of structural chromosome change in which all of the genetic material is present, but its location or orientation has changed. Cytogenetics laboratories commonly identify carriers of balanced chromosome rearrangements, most often translocations, due to either multiple pregnancy loss, infertility, or by chance during prenatal diagnostic studies. In the last case, a balanced rearrangement discovered in a fetus is found to be inherited from one of the parents. Such a rearrangement does not entail an increased risk for physical or mental abnormality to the fetus. The carrier of such a rearrangement is, however, at an increased risk for a chromosomally unbalanced fetal karyotype detected at prenatal diagnostic studies or at birth. The actual level of risk depends on the method of ascertaining the rearrangement (the previous birth of a liveborn chromosomally unbalanced child carries the highest risk) and on the precise nature of the chromosome change (the smallest amount of imbalance carries the highest risk). Several schemata for calculating such risks have been developed.[33,34]

A more difficult counseling issue arises when an apparently balanced rearrangement is discovered de novo at the prenatal diagnosis. Within institutions for the mentally handicapped, when persons with known clinical diagnoses are eliminated from consideration, about a tenfold higher incidence is found of apparently balanced rearrangements than in the general population.[35] This information, however, simply indicates that there is an increased risk to the fetus discovered to carry such a translocation. The biased data set cannot provide an actual risk figure. As was the case for marker chromosomes, only prospective data gathered at prenatal diagnostic studies with proper follow-up are suitable for calculating the risk. Data of Warburton collected from cytogenetics laboratories throughout the United States and Canada suggest a risk for a fetal abnormality of between 3% and 10% (to be compared with the usual estimate of 2% to 3% for congenital malformations at birth in the general population).[28] The mechanism(s) responsible for the increased risk associated with apparently balanced rearrangements is unknown. The abnormal clinical features, often mental retardation without major dysmorphic findings, are not those that would be expected if the chromosome breaks associated with the translocations were causing new dominant mutations. It may be that the rearrangements are not truly balanced, but have caused a loss or gain of genetic material not visible at the cytogenetic (light-microscopic) level or that the actual position of the genetic material, and not solely its content, is critical.

Analysis of Genetic Diseases With Cytogenetic Manifestations

To this point, discussion has focused on indications for, and interpretations of, cytogenetic studies related to the determination of a fetal karyotype. Such studies represent the great majority of all prenatal cytogenetic analyses. For several inherited genetic diseases, however, though the risk for a karyotypic abnormality is not increased, cytogenetic methods are used in prenatal (and postnatal) diagnostic studies. Cells of affected persons show either generalized or site-specific effects on chromosomes through which the diseases may be diagnosed.

Chromosome Breakage Disorders

A series of three relatively rare autosomal recessive diseases are usually classified together as the "chromosome breakage disorders." They are the Bloom syndrome, Fanconi's anemia, and ataxia telangiectasia. Although the actual clinical presentations of the diseases differ markedly one from the other, all share a tendency toward spontaneous chromosome breakage (with different patterns in each disease) and a predisposition toward the early development of cancers (of different types in each disease).[36] Analysis for the Bloom syndrome is aided by a tendency of chromosomes from patients to show greatly increased numbers of "sister chromatid exchanges."[37] Special culture conditions and staining techniques are required to visualize sister chromatid exchanges. Prenatal diagnostic studies for ataxia telangi-

ectasia take advantage of a hypersensitivity to x-ray induced damage, whereas those for Fanconi's anemia rely on hypersensitivity to a class of chemical mutagen known as alkylating agents.[38,39] Because the successful treatment of persons affected by Fanconi's anemia often depends on the presence of an HLA-identical hematopoietic stem cell donor, families with an affected child will usually have the option to have HLA typing as well as prenatal diagnostic studies in future pregnancies. Cord blood collected from HLA-identical unaffected siblings provides an excellent source of donor cells.[40]

Roberts's Syndrome

Another recessively inherited disorder, Roberts-SC phocomelia syndrome (or pseudo-thalidomide syndrome), usually lethal in the prenatal or neonatal period, is characterized by severe limb reduction abnormalities and, when measurable, profound mental retardation. (There are reports of less severely affected persons; it is unknown if these represent mutations at the same genetic locus as those with the more severe manifestations.) By cytogenetic analysis, Roberts's syndrome is recognized by an apparent repulsion of sister chromatids at blocks of heterochromatin (noncoding regions), usually near the centromeres. This, combined with ultrasonographic findings, serves as an effective means for prenatal diagnosis of the disorder.[41]

Fragile X Syndrome

The fragile X-linked mental retardation syndrome represents the single most common genetically inherited mental retardation syndrome and, after the Down syndrome, the single greatest contributor to mental retardation in the population. Readers are referred to an excellent recent review of its clinical, genetic, and molecular details.[42] The disease received its name from its association with an inducible "fragile site" near the end of the long arm of the X chromosome. The site is induced through the manipulation of cell culture conditions and is expressed in a variable percentage of cells from most affected and some carrier persons. With the cloning of the gene for this disorder (*FMR1*, for fragile X-linked mental retardation-1), that approach has been largely superseded by molecular technologies involving the direct analysis of the gene. Such technologies have greatly aided carrier testing and prenatal diagnostic studies. Mention of the disease is included here both for historical reasons and because there remains some use of the cytogenetic methods in the prenatal assignment of risk for mental retardation for female carriers of the "full mutation" for fragile X (the mutation exists in "premutation" and "full mutation" forms).[43]

Conclusions

Cytogenetic analysis due to an increased risk for nondisjunction is the most commonly used method requiring invasive procedures for prenatal diagnosis. Highly accurate and successful systems for such analyses are established, and developments in molecular genetics have become well integrated into those systems. That integration continues to shed new light on old problems and to allow the introduction of entirely new approaches to prenatal diagnosis. The analysis of fetal cells in maternal circulation holds promise of fundamentally changing access to these services and of perhaps necessitating a serious look at the question of whether full karyotypic analysis should remain the standard of practice over the long term. These developments promise an exciting future in both the diagnostic-research and the medical-societal arenas.

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Prenatal Diagnosis and Significance of Fetal Infections

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Viruses like rubella, cytomegalovirus, varicella-zoster virus and parasites like *Toxoplasma gondii* can be transmitted from a pregnant woman to her fetus and can affect fetal development. Several factors determine the likelihood of fetal infection and the risk of consequences for the fetus, such as the timing of transmission during gestation or the immunologic status of the mother. No single diagnostic modality can be applied to all infections. Knowledge of the diagnostic methods available is essential for accurate counseling and treatment of affected pregnant women.

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Maternal infection can lead to fetal infection by hematologic spread to the placenta and hence to the fetus. As a consequence of this route of infection, the infection can be limited to the placenta or both placenta and fetus can be infected. The timing and extent of fetal infection following maternal infection can vary, depending on the type of infection, the gestational age at infection, and the immunologic status of the mother. Evidence of fetal infection relies on the identification of the organism or detection of its antigens or genome in fetal compartments (amniotic fluid, fetal blood, or ascitic fluid) or the detection of specific immunoglobulin (Ig) M antibodies targeted to the offending organism in the fetal blood or amniotic fluid. Identifying an infectious agent can sometimes take weeks, however. The production of specific IgM antibodies depends on the maturity of the fetal immune system and the immunogenicity of the specific infectious agent. Therefore, the detection of specific IgM antibodies is reliable evidence of fetal infection, but their absence does not rule it out. Nonspecific evidence of fetal infection can also be obtained from fetal blood sampling—elevated total IgM antibodies, thrombocytopenia, eosinophilia, and elevated liver enzyme levels—and although not diagnostic, it increases the likelihood of fetal involvement in the presence of a documented recent maternal infection.

The most common pathogen transmitted in utero is cytomegalovirus (CMV), with an incidence of about 1% to 2% of pregnancies. *Toxoplasma gondii* infects about 4 of 1,000 pregnant women per year, causing congenital infection in 3,700 of the 3.7 million infants born a year in the United States. Every year 1,500 cases of varicella-zoster virus infection during pregnancy are reported in this country. The occurrence during pregnancy of rubella virus infection, once an important causative agent of congenital malformations, has substantially decreased, thanks to a general program of vaccination, but 21 infants were born with the rubella syndrome in southern California during 1990.[1] The incidence of parvovirus B19 infection in pregnancy is unknown, but it is probably rare.[2] Each year in the United States, about 6,000 pregnant women infected with the human immunodeficiency virus type 1 (HIV-1) deliver, and although the virus is not teratogenic, infected newborns succumb within a few years of life to opportunistic infections. For many of the specific infections discussed in this article, few data are available in the literature, and specific recommendations cannot be made.

Cytomegalovirus Infection

Like other herpesviruses, CMV can cause primary and recurrent infections. About 50% to 85% of women of reproductive age show serologic evidence of a previous CMV infection. The attack rate among susceptible women is about 2% per year among women at a higher socioeconomic level, compared with a 6% annual attack rate among women of lower income.[3]

Fetal CMV infection can follow either a primary or reactivated maternal infection. From 30% to 40% of pregnant women with primary CMV infection transmit the virus to their fetuses; 10% of these fetuses will be symptomatic at birth, and the infection will result in neonatal death or mental retardation and neurologic problems in most of the survivors. Of the 90% asymptomatic infected fetuses, 5% to 15% will have long-term neurologic sequelae develop later in childhood, usually in the form of

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Reprints are not available.

ABBREVIATIONS USED IN TEXT

AIDS = acquired immunodeficiency syndrome
CMV = cytomegalovirus
HIV-1 = human immunodeficiency virus type 1
Ig = immunoglobulin
PCR = polymerase chain reaction

a mild to profound hearing loss. Gestational age at the time of maternal infection does not affect the transmission rate, but it seems to influence the severity of the infection, with most symptomatic infants being born to women who acquire CMV infection in early gestation.[3] Among women with immunity to CMV, about 0.5% to 1% have a recurrent infection during pregnancy. Preexisting maternal antibodies to CMV seem to protect the fetus, however, and lessen the incidence and severity of the manifestations of congenital CMV infection.

A recent study has compared the outcomes of 125 CMV-infected infants born to women who acquired primary infection during pregnancy with those of 64 CMV-infected infants born to women with recurrent infection during pregnancy.[4] At birth, 18% of the infants in the primary-infection group had symptomatic CMV infection compared with none in the recurrent-infection group. After a mean follow-up of 4.7 years, one or more sequelae were seen among initially asymptomatic infants in 25% of the primary-infection group compared with 8% of the recurrent-infection group ($P = .003$), including mental retardation in 13% versus 0% and hearing loss in 23% versus 5%, respectively.

The diagnosis of in utero infection after a documented maternal infection requires a combination of ultrasonography and invasive procedures, such as amniocentesis and fetal blood sampling. By compiling the series published in the literature,[5-7] we found a total of 24 cases that have been evaluated after primary maternal CMV infection and after routine serologic screening. Fetal infection was documented in 11 cases and excluded in the rest (Table 1). In these patients, the detection of CMV early antigens and culture of the virus from amniotic fluid were the most reliable diagnostic tests. A fetal blood specimen obtained by cordocentesis can be tested for specific IgM antibodies and for nonspecific signs of in utero infection, such as anemia, thrombocytopenia, elevated leukocyte counts or total IgM levels, or abnormal liver function test results. Specific fetal IgM antibodies were present in only five (63%) of eight fetuses, and fetal blood culture grew CMV in one (13%) of the eight cases in which fetal blood sampling was done. On ultrasound examination, intrauterine CMV infection may present as ascites or generalized hydrops, ventriculomegaly, intracranial calcifications, increased bowel echodensity, and growth retardation.[5,8] All fetuses at risk with abnormal sonographic findings have been found to be infected.[5,6,8-10] The converse is not true, however: the absence of abnormal sonographic findings does not rule out infection in a fetus.

Pregnant women with documented seroconversion to CMV should be offered amniocentesis for viral identification. Fetal blood sampling can be offered if other potential prognostic indicators—total IgM antibody titers, hematologic indices, and liver function tests—are desired. In the absence of ultrasonographic findings, we are unable to predict which fetuses will be clinically affected. The CMV genome can be detected by hybridization or polymerase chain reaction (PCR),[11] but these techniques are currently used only on an investigational basis.

Ganciclovir, with or without CMV-hyperimmune globulin, has been used with success in the treatment of adults and neonates with CMV infection.[12] It may decrease viral shedding and reduce the risk of organ damage in cases of in utero infection. Before this is attempted, larger trials evaluating the clinical efficacy and safety in newborns will be necessary.

Toxoplasmosis Infection

Toxoplasma gondii is a protozoan transmitted by oocysts in cat feces, infected meat eaten raw or inadequately cooked, and unwashed vegetables and fruit. Acute infection is asymptomatic in almost 90% of patients. After host cell invasion, *T gondii* forms cysts in all tissues (most commonly in the brain, skeletal muscles,

TABLE 1.—*Prenatal Diagnosis of Cytomegalovirus (CMV) Infection in 11 Infected Fetuses*

Fetus	Source	Early Antigen Detected in Amniotic Fluid	CMV in Culture: Amniotic Fluid	CMV in Culture: Fetal Blood	Ultrasonographic Findings	Fetal CMV IgM	Aspecific Findings	Outcome
1	Lynch et al, 1991[5]	Yes	Yes	Yes	Normal	No	Yes	Pregnancy terminated
2	Hohlfeld et al, 1991[6]	Yes	Yes	No	Ascites	Yes	Yes	Pregnancy terminated
3		Yes	Yes	No	Normal	Yes	Yes	Pregnancy terminated
4		Yes	Yes	No	Normal	Yes	Yes	Neonatal infection
5		Yes	Yes	No	Normal	Yes	Yes	Subclinical infection
6		Yes	Yes	No	Normal	Yes	Yes	Pregnancy terminated
7		Yes	Yes	No	Normal	No	Yes	Subclinical infection
8		Yes	Yes	No	Normal	No	No	Subclinical infection
9	Skvorc-Ranko et al, 1991[7]	NA	Yes	NA	NA	NA	NA	Subclinical infection
10		NA	Yes	NA	NA	NA	NA	Subclinical infection
11		NA	Yes	NA	NA	NA	NA	Subclinical infection

NA = not available

and heart), where it persists for the life of the host. Reactivations with parasitemia are possible in immunocompromised patients.[13] About 40% of pregnant women in the United States are immune to toxoplasmosis.[14] About 4 of 1,000 susceptible pregnant women will acquire toxoplasmosis during the nine months of gestation. Because 40% of such women, if not treated, will give birth to infected infants, the annual incidence of congenital infection is 1 to 2 per 1,000.

A diagnosis of recent *T gondii* infection can be made in the presence of documented seroconversion from a negative to a positive titer; specific IgM antibodies, even though there are substantial individual variations in response to infection (in many cases immunocapture methods can detect IgM antibodies more than a year after the acute infection)[15]; or a fourfold increase in specific IgG titer when sampling is done at three-week intervals in the absence of treatment. A serologic diagnosis requires a careful interpretation of the results because some tests have different sensitivities at various stages of infection. It is important to rely on a reference laboratory where several tests can be done in parallel with evaluations of previous specimens. There is as yet no consensus on whether routine testing for toxoplasmosis in pregnancy is cost-effective.

Vertical transmission occurs only during maternal parasitemia, hence during acute infections or reactivated latent infections in immunocompromised persons. Infection of the placenta is an obligatory step for maternal-to-fetal transmission. Once the placenta becomes infected, it remains so for the duration of the pregnancy. The delay between maternal and fetal infection varies from less than 4 weeks to more than 16 weeks.[16] The transplacental passage increases with the gestational age: only 1.2% of fetuses are infected when maternal infection occurs around the time of conception, whereas the incidence of fetal infection increases to 4.5% if the mother was infected at 6 to 16 weeks, 17.3% if infected at 17 to 20 weeks, and 28.9% if infected after midgestation.[17] The incidence of severe fetal infection, however, decreases from about 75% during first-trimester maternal infection to almost 0% for transmission during the third trimester.[18]

Overall, 20% to 30% of untreated infected neonates are symptomatic at birth (convulsions, spasticity, hypotonia, chorioretinitis, encephalitis, hydrocephalus, microcephaly). Among asymptomatic neonates, chorioretinitis will develop in almost all untreated persons by adulthood, and about 50% will have severe visual impairment.[19] Antibiotic treatment for a year after birth is currently recommended, but it has not been determined whether treatment improves the long-term outcome.[19] The visualization of intracranial calcifications or hydrocephalus by ultrasonogram is not only diagnostic of fetal infection but also suggestive of severe fetal involvement.

As soon as the diagnosis of recently acquired toxoplasmosis is made or suspected in a pregnant woman who desires the continuation of her pregnancy, antibiotic treatment should be started to reduce the probability of the transmission of parasites to the fetus. At the same time, further evaluation can be carried out to determine whether the fetus is already infected. A combination of amniocentesis, ultrasonography, and fetal blood sampling can lead to a correct diagnosis of fetal infection in about 92% of cases.[20] The sensitivity and specificity of the different diagnostic tests are shown in Table 2. With the absence of false-positive results, fetal blood sampling is diagnostic of congenital toxoplasmosis when specific signs of infection, such as *T gondii* IgM titers or parasites, are detected. Amniocentesis is diagnostic of fetal infection if the parasite is identified in amniotic fluid. The identification of *T gondii* by mouse inoculation requires three to six weeks; fibroblast cell culture requires less than a week, but it is less sensitive.[21] Preliminary data show that PCR amplification for detecting the *T gondii* genome is the most sensitive and specific test,[22,23] but its use is currently limited to research centers.

TABLE 2.—*Accuracy of Diagnostic Tests for Congenital Toxoplasmosis**

Test	*Sensitivity, %*	*Specificity, %*
Fetal blood sampling		
Identification of parasites in fetal blood	64	100
Elevated γ-glutamyltransferase	57	97
Total IgM	52	97
Elevated leukocyte count	38	97
Low platelet count	28	98
Specific IgM antibodies	21	100
Elevated eosinophil count	19	94
Elevated lactate dehydrogenase	17	98
Amniocentesis	52	100
Ultrasonogram	45	99.8

*Modified from Daffos et al.[20]

The treatment of a woman during pregnancy substantially reduces the likelihood of fetal infection. Spiramycin has few maternal side effects, no teratogenic action, but scarce transplacental passage, so that its therapeutic effect consists mainly of preventing the parasites from crossing the placenta. A more aggressive antibiotic treatment with sulfonamides and pyrimethamine can alternatively be used, and their use has been recommended in cases of documented vertical transmission to decrease the severity of fetal infection. In a large series from France, 16 (14%) of 116 untreated women had infants severely affected at birth, compared with 3 (4%) of 79 women treated with a combination of sulfonamides-pyrimethamine and spiramycin.[24] In a more recent series, the incidence of the presence of specific IgM antibodies and of clinical infection was considerably lower among newborns whose mothers were treated with a combination of pyrimethamine-sulfadiazine and spiramycin, compared with newborns whose mothers received spiramycin alone.[25]

Varicella-Herpes Zoster Virus Infection

The varicella-zoster virus is a member of the herpesvirus family. The incubation period is 15 ± 5 days, and

it is contagious between two days before and five days after the outbreak of the rash. About 95% of adults are immune. Subclinical infection is uncommon. The incidence of varicella infection in pregnancy is about 1 in 2,000 pregnancies, whereas that of herpes zoster is 1 in 10,000. Evidence of fetal infection following maternal varicella is seen in 24% of cases,[26] but it is rare after maternal herpes zoster, probably because the latter is rarely associated with viremia.

A well-recognized "congenital varicella syndrome" (also called varicella embryopathy) has been described in a small proportion of infected fetuses. Pooling of the data from several prospective studies indicates that the risk of the congenital varicella syndrome is 1.8% (3/167) if maternal infection occurs during the first trimester and less than 1% if it occurs after the first trimester.[26-30] In all, 36 cases of the syndrome have been reported.[31-38] Anomalies included cicatricial skin lesions (usually conforming to a dermatomal distribution), limb abnormalities (hypoplasia, contractures), ocular abnormalities (chorioretinitis, microphthalmia, cataracts), and neurologic abnormalities (including peripheral, central, and autonomic nervous systems: paralysis, seizures, microcephaly, hydrocephaly). It has been suggested that the fetal abnormalities are not due to direct damage from the varicella, but to in utero reactivation of the infection leading to fetal herpes zoster.[32] A latency period of at least five weeks between maternal infection and fetal abnormalities has been documented in cases detected in utero by ultrasonography.[36] About a third of infants with the congenital varicella syndrome die in the neonatal period, and most survivors have substantial sequelae.[39]

The prenatal diagnosis of the congenital varicella syndrome is challenging. Chorionic villus sampling and the PCR technique have been used in two cases to document placental infection, but neither of the two fetuses appeared to be infected.[40] Ultrasonography has shown abnormalities in eight of nine fetuses later diagnosed with the fetal varicella syndrome (Table 3)[31,33-36,41]; the most common findings were polyhydramnios, liver hyperechogenicities, and fetal hydrops. The detection of viral DNA in amniotic fluid by the PCR technique may prove to be a sensitive indicator of fetal infection, but it awaits further investigation.

Fetal blood sampling has limited application because viremia is present for a limited time, and specific fetal IgM is absent in more than half of infected newborns. One case of successful prenatal diagnosis by fetal blood sampling has been reported: the mother had been infected at 20 weeks, and fetal blood sampling at 32 weeks revealed specific IgM and high total IgM titers.[31]

Varicella-zoster immune globulin prevents clinical varicella when given to susceptible persons within 96 hours of exposure. It should be given to pregnant women who have had exposure to the virus who are without evidence of or with unknown immunity and neonates whose mothers had varicella within a few days of delivery. Neonatal mortality in this situation can be high because synthesis and the transplacental passage of specific maternal IgG have not had time to occur. Acyclovir treatment should be considered when delivery is anticipated within a few days of maternal infection. The drug crosses the placenta, may inhibit in utero viral replication, and may lessen the severity of postnatal disease. There is no evidence, however, that varicella-zoster immune globulin, acyclovir, or interferon treatment can alter the course of intrauterine infection or prevent fetal infection.

Rubella Infection

Rubella is an RNA virus without a serologic relationship to other known viruses that can affect humans. Infection is asymptomatic in 25% to 50% of cases. In developed countries, only 5% to 20% of women of reproductive age are susceptible to the virus. Despite a program of rubella screening and vaccination in women, the number of reported cases of rubella infection in the general and in the obstetric populations of the United States has recently increased.[1,42] Past rubella infection can be diagnosed by the detection of specific IgG antibodies, whose presence correlates with protective immunity. Recent infection is documented by the presence of specific IgM antibodies that can be detected shortly after the onset of illness; their levels peak at seven to ten days, and they persist as long as four weeks after the appearance of the rash.[43]

TABLE 3.—*Sonographic Findings in Fetuses With the Congenital Varicella Syndrome*

Fetus	Source	Gestational Age, wk: At Exposure	Gestational Age, wk: At Ultrasonogram	Sonographic Findings	Outcome
1	Alexander, 1979[41]	16	31	Polyhydramnios	Neonatal death
2	Cuthbertson et al, 1987[31]	20	32	Polyhydramnios, hydrocephaly	Neonatal death
3	Harding and Baumer, 1988[33]	14	17	Normal	Neonatal death
4	Scharf et al, 1990[34]	14	28	Polyhydramnios, hydrocephaly, clubfeet	Neonatal death
5	Byrne et al, 1990[35]	15	30	Liver hyperechogenicity, polyhydramnios	Alive
6	Pretorius et al, 1992[36]	16	35	Polyhydramnios	Neonatal death
7		16	24	Polyhydramnios, hydrops, liver hyperechogenicity	Neonatal death
8		13	32	Polyhydramnios, liver hyperechogenicity	Neonatal death
9		14	19	Hydrops, arthrogryposis, liver hyperechogenicity	Neonatal death

Subclinical reinfection is possible, both after natural infection and after vaccination. It is diagnosed serologically by a notable (greater than fourfold) increase in antibody concentration or the detection of IgM antibodies in a person with known rubella antibodies.[44] The incidence of vertical transmission (fetal infection rate) declines from 90% during the first trimester to 25% at the end of the second trimester, and then rises again to 95% to 100% during the last month of pregnancy.[45,46] During the first trimester, the risk of fetal infection is nonexistent when the maternal rash appears within 12 days from the last menstrual period, increases to 31% when the rash occurs 12 to 21 days from the last menstrual period, and is 100% in cases of maternal infection 3 to 6 weeks from the last period.[47]

The risk of fetal damage in cases of fetal infection decreases from almost 100% during the first trimester to 35% during the early second trimester (Table 4).[45,47-49] No severe damage has been observed after the 17th week of pregnancy, with these children presenting with only subclinical forms of congenital rubella.[49] Long-term studies on these cases are not available. No cases of fetal damage after maternal vaccination in pregnancy have been reported, even though theoretic concerns still contraindicate rubella vaccination during pregnancy.

The most commonly described anomalies associated with the congenital rubella syndrome are ophthalmologic (cataracts, microphthalmia, glaucoma, chorioretinitis), cardiac (patent ductus arteriosus, pulmonary artery stenosis, atrial or ventricular septal defects), and neurologic (sensorineural deafness, microcephaly, mental retardation). In addition, most affected infants have retarded growth and nonspecific findings of congenital infection (hepatosplenomegaly, thrombocytopenia). Milder cases may go unrecognized for months or even years after birth.

The termination of pregnancy should be offered in cases of maternal infection at between 3 and 10 weeks' gestation. The rate of fetal infection and birth defects is lower from 11 to 18 weeks, and the option of a prenatal diagnosis should be offered to these patients. This has been accomplished by the detection of specific IgM in fetal blood. Fetal IgM can be synthesized from the 12th week of gestation, but is consistently found only after the 22nd week in cases of rubella infection.[50] The overall sensitivity of prenatal diagnosis in the largest series available (n = 119) has been 98% (59/60), with specificity of 100% (59/59).[50] The only incorrect diagnosis (false-negative) was thought to be due to sampling too early during pregnancy (20 weeks). The virus can also be isolated from the amniotic fluid and grown in primary cell cultures,[7,51-53] but the method is insensitive and time consuming (up to six weeks). Alternatively, viral RNA can be detected by in situ hybridization or PCR,[54-56] but the accuracy of these newer techniques is unknown. Because all infected fetuses produce IgM, this method cannot be used to differentiate fetuses who are clinically affected from those who are unaffected. Given the rarity of fetal sequelae when infection occurs after midgestation, terminating the pregnancy or doing invasive diagnostic studies to detect fetal infection is not recommended.

Immune globulin therapy after exposure to rubella early in pregnancy does not prevent fetal infection or teratogenic effects. Its use can be considered only when a pregnant woman with exposure to rubella would not consider terminating the pregnancy under any circumstances.[45] No antiviral treatment is yet available or tested.

Human Parvovirus B19 Infection

The most common clinical manifestations of B19 infection are erythema infectiosum, arthralgias, or arthritis, with low-grade fever and flulike symptoms. Parvovirus B19 infection can be entirely asymptomatic in about 20% of women. It is common in childhood, and nearly 50% of women at childbearing age are immune.[57] The attack rate among susceptible household contacts is about 50%, and during school outbreaks, the transmission of infection to susceptible teachers is about 20%.[58]

The primary sites for B19 replication are the erythroid progenitor cells in the bone marrow. The infection is lytic in nature, leading to erythrocytes failing to mature. The

TABLE 4.—*Fetal Infection Rates After Confirmed Maternal Rubella Infection**

Gestational Age, wk	*Fetal Infection, No. Infected/No. Exposed (%)*	*Rubella-Associated Defects/ Seropositive Infants, No./No. (%)*	*Overall Risk†*
2-3	4/13 (31)	NA	NA
4-6	10/10 (100)	11/11 (100)	100
7-10	9/9 (100)	24/29 (83)	83
11-12	8/13 (62)	20/25 (80)	55
13-14	16/25 (64)	16/31 (52)	33
15-16	24/46 (52)	17/38 (45)	23
17-20	13/33 (39)	2/33 (6)	2
21-23	6/35 (17)	0/16 (0)	0
24-30	19/63 (30)	(0)	0
31-36	15/25 (60)	(0)	0
>36	8/8 (100)	(0)	0

NA = not available

*From Miller et al,[45] Enders et al,[47] Munro et al,[48] and Grillner et al.[49]
†The overall risk was calculated as follows: % seropositive fetuses with defects × % infants infected.

aplastic event lasts seven to ten days, after which time reticulocytes appear; the bone marrow fully recovers within about three weeks. Adults with normal hematopoiesis tolerate this transient red cell aplasia with a minimal decrease in hemoglobin; however, anemia may develop in cases of infection when there is rapid erythrocyte turnover (as in fetuses).

The mainstay of the diagnosis of B19 infection in pregnant women with exposure to parvovirus or with symptoms of infection is the use of serologic tests. B19-specific IgM antibodies appear within 3 days after the illness begins, but persist for only 30 to 60 days; specific IgG antibodies appear after a week and can be used to document recent infection if both acute and convalescent sera are tested simultaneously and display a substantial rise in antibody titers. The B19 virus cannot be cultured on traditional tissue culture media. In the fetus, viral particles can be identified in fetal tissues (ascitic fluid),[59] or viral DNA can be detected by either in situ hybridization or Southern blot techniques.[59-61] Parvovirus B19 DNA probes are most useful during the acute viremic phase of the infection and may show normal findings after symptoms resolve.[62]

Recently, DNA amplification by PCR has been used that allowed the detection of viral DNA in amniotic fluid,[63] but this technique is currently available in only a few research laboratories. Specific fetal IgM antibodies can also be detected in amniotic fluid or umbilical cord blood.[53] Amniocentesis and fetal blood sampling are indicated in the presence of hydrops. Amniocentesis is not yet recommended in all cases of maternal B19 infection because of the lack of a laboratory willing to do viral identification by the PCR technique in amniotic fluid.

The transplacental transmission rate of B19 has been estimated to be 33%.[2] It has been estimated that the risk of fetal death due to B19 infection is about 9%.[2] Preliminary data from a prospective cohort study of about 200 women with serologic evidence of acute B19 infection indicate that there is a 2% to 3% increase in fetal deaths among infected women compared with controls.[64]

Parvovirus B19 infection can jeopardize a fetus at any gestational age. Severe anemia and hydrops precede fetal death in most cases.[61] When present, hydrops generally occurs 3 to 5 weeks after symptomatic infection in the mother, but it has been reported as long as 12 weeks later.[2,61] Therefore, once maternal infection has been documented, serial sonographic examinations every one to two weeks are indicated to detect early signs of hydrops. Surveillance should be started as early as possible because hydrops due to B19 infection has been seen as early as 11 weeks' gestation.[2] Some fetuses can become hydropic without evidence of anemia: because viral particles have been recovered from the myocardium, in these cases hydrops has been thought to be due to cardiomyopathy.[63,65,66]

Although most fetuses with hydrops die in utero if not transfused, cases of transient hydrops and survival without therapeutic intervention have been reported.[62,67,68] It is unclear whether in utero transfusion improves fetal outcome. Infants who survive the severe anemia with or without in utero transfusion appear to develop normally. There is no conclusive evidence that B19 infection is associated with anatomic abnormalities. The efficacy of maternal prophylactic immune globulin administration after exposure has not been determined yet, and its use is not recommended at this time. A vaccine is not available, but its implementation should be made easier by the antigenic stability of B19 virus.

Human Immunodeficiency Virus Type 1 Infection in Pregnancy

About 6,000 HIV-1-positive women give birth in the United States during a 12-month period.[69] Modes of infection in women include injection drug use (52%), heterosexual transmission (33%), and exposure to blood products, but a substantial proportion of infected women do not acknowledge risky behaviors. Pregnancy does not seem to be associated with an accelerated progression of HIV-1 disease.[70]

Data from several prospective studies show that vertical transmission rates range between 13% and 30% of cases.[71-73] The risk of infection appears to be greatest for infants born to women with advanced infection (such as those with the acquired immunodeficiency syndrome [AIDS], with $CD4^+$ counts during the third trimester below 700×10^6 per liter [700 per μl], or with evidence of p24 antigen in the blood) and for those delivered before 34 weeks of gestation.[71] Even though fetal infection during the second trimester has been documented,[74,75] recent findings strongly suggest that in a significant proportion of cases, HIV-1 is transmitted from mother to infant at the time of delivery: indeed, for twins born to HIV-infected mothers, the first child delivered, either vaginally or by cesarean section, is more likely to be HIV-infected than the second one.[76] If HIV-1 were transmitted across the placenta earlier in pregnancy, birth order should make no difference in the infection rate. Episiotomy, the application of scalp electrodes, and instrumental deliveries were associated with an increased risk of transmission only in centers where these procedures were not routinely used.

Prenatal diagnosis is not recommended as invasive procedures like fetal blood sampling may theoretically introduce the virus into a previously uninfected fetus. The magnitude of this risk is unknown. Furthermore, a fetus may become infected anytime after prenatal diagnosis because maternal viremia persists. Fetal HIV-1 infection does not seem to be associated with a substantially increased incidence of intrauterine growth retardation, prematurity, microcephaly, or dysmorphism once other confounding variables are taken into account.[71,77,78]

The mainstay of the treatment of nonpregnant women with AIDS, AIDS-related complex, or $CD4^+$ cell counts of less than 200×10^6 per liter rests on antiretroviral therapy with zidovudine and *Pneumocystis carinii* pneumonia prophylaxis with the combination drug trimethoprim and sulfamethoxazole.

Because of the lack of solid data on the fetal side effects and toxicities, the Public Health Service has avoided

recommending therapies in pregnancy, but as there are no adverse fetal effects known to outweigh the maternal benefits of these therapies, they should not be withheld during pregnancy.[79] Most obstetricians offer zidovudine treatment to pregnant women in advanced stages of disease, avoiding its use during the first trimester because of possible teratogenic risks.

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Prenatal Diagnosis of Inherited Metabolic Diseases

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Advances in the prenatal diagnosis of inherited metabolic disease have provided new reproductive options to at-risk couples. These advances have occurred in both sampling techniques and methods of analysis. In this review we present an overview of the currently available prenatal diagnostic approaches for the diagnosis of metabolic disease in a fetus.

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The prenatal diagnosis of inherited metabolic disease has offered at-risk couples the opportunity to plan to have only unaffected offspring. For some disorders, such as phenylketonuria and galactosemia, prenatal diagnosis may also provide for the early institution of therapy in the neonatal period. Because many of these couples have learned of their at-risk status only as a result of having a previous affected offspring, they are acutely aware of the difficulties involved in having another affected infant. For other couples, their at-risk status has been determined by carrier screening. Before the availability of prenatal diagnosis, many couples opted to simply not have any more children. Prenatal diagnosis has provided additional reproductive options for these couples.

Before attempting the prenatal diagnosis of any inherited disease, it is essential to establish or confirm the specific diagnosis of the disorder under consideration. Efforts must be directed toward eliminating the possibility of misdiagnosis due to phenotypic, metabolic, or genetic heterogeneity. In the case of an enzymatic or molecular diagnosis, the precise defect must be demonstrated in the proband or affected relatives. If the proband is deceased, the heterozygosity of both parents (or of the mother for an X-linked disease) must be documented.

The area of prenatally detecting metabolic diseases is a constantly evolving one. New laboratory techniques are being developed and new sampling approaches being tried. In addition, as more disorders are characterized on a DNA level, molecular techniques are increasingly being applied. In this review we will provide an overview of both the current analysis techniques and available sampling methods, with emphasis on the advantages and limitations.

Procedures for Fetal Sampling

The demonstration of a metabolic defect requires removing fetal material for biochemical or molecular analysis. In the past, most prenatal diagnoses of metabolic disorders have been done through a biochemical analysis of cultured amniotic fluid cells. Today, other sampling techniques are feasible for obtaining fetal material. The choice of which technique to use depends mainly on the availability of a reliable test—enzymatic, DNA—that can be done on the specific fetal tissue (amniotic cells, trophoblast, blood, liver cells). When a reliable test is feasible for different materials, the decision of which sampling procedure to use depends on the gestational age, the risk of miscarriage due to the procedure, the operator's skill and experience, and the woman's preference.

Amniocentesis and Early Amniocentesis

Amniocentesis under the guidance of ultrasonography is a well-established and reliable procedure, with a risk of miscarriage of about 0.5% in centers with experienced staff.[1] A specimen of about 20 ml of amniotic fluid is removed by transabdominal puncture at 15 to 18 weeks' gestation, the optimal time with regard to cell number and viability.

Because of the relatively late gestational age when amniocentesis has traditionally been performed, investigation has begun into early amniocentesis.[1,2] This procedure is offered to women who are pregnant between 12 and 15 weeks. Results relating the complication rates of early amniocentesis so far are conflicting. In addition, there is no clear evidence if there is a substantial difference in growth between cells obtained early and those obtained at the traditional time.[3] The ontogeny of enzyme expression must also be observed in amniocytes obtained from early amniocentesis. The specific abnormality under investigation must be shown to be present at the gestational age the procedure is done.

The prenatal diagnosis of metabolic diseases using early amniocentesis has been reported for methylmalonic acidemia, propionic acidemia and argininosuccinicacide-

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ABBREVIATIONS USED IN TEXT

CVS = chorionic villus sampling
PCR = polymerase chain reaction
RFLP = restriction fragment length polymorphism

mia, mucolipidosis II (I-cell disease), Sandhoff disease, Niemann-Pick disease, mucopolysaccharidosis type II, Krabbe's disease, cystic fibrosis, and Duchenne-type muscular dystrophy.[2,4-6]

Although many disorders can now be diagnosed in the first trimester using chorionic villus sampling (CVS), midtrimester amniocentesis is still widely used as the primary procedure and in some situations for confirming a diagnosis done in the first trimester by CVS. Table 1 lists the metabolic diseases that can be diagnosed prenatally.

Uncultured Amniotic Cells

Most assays are performed on fibroblasts from amniotic cell culture. The use of uncultured amniotic cells or cell-free amniotic fluid has been reported for diagnosing several inborn errors of metabolism by identifying the specific enzyme or metabolites.[7] The use of uncultured amniotic cells has several problems, and particular care is required in interpreting the data from these sources. Many of the amniotic cells are dead and in various states of decay and may give low specific activities. Uninterpretable values and false-positive and -negative diagnoses can be due to the admixture of fetal and maternal cells.

The potentially more rapid approach using uncultured amniotic fluid cells is unreliable at this time. The extraction and amplification of DNA from uncultured amniotic cells using the polymerase chain reaction (PCR) is a new approach suitable for prenatal diagnosis from eight weeks' gestation and on and will be discussed later in this review.

Cell-Free Amniotic Fluid

The direct chemical analysis of metabolites using cell-free amniotic fluid obtained at 12 to 18 weeks of pregnancy offers the advantage of a rapid and reliable prenatal diagnosis. Clearly if a metabolic disorder can be diagnosed using fluid only, the delays involved using cell culture are avoided. The method can be used only when unambiguous discrimination is achieved between normal levels of a metabolite and the elevated levels observed in affected cases.

The levels of soluble enzymes or metabolites in amniotic fluid vary widely at different gestational ages and must be compared with values from an adequate number of normal control specimens matched for gestational age. Most soluble proteins in amniotic fluid have a maternal origin and are therefore inappropriate for prenatal diagnosis. A few proteins of fetal origin can be used as indicators of fetal abnormality.

Amniotic fluid concentrations of metabolites have been investigated for conditions like 21-hydroxylase deficiency in which excess quantities of a metabolite are excreted by the fetus due to a metabolic block.[8] The technique is particularly well suited for the prenatal diagnosis of organic acidurias[9,10] in which high concentrations of specific metabolites accumulate in the urine. Similarly, abnormal metabolites produced by the fetus can accumulate in amniotic fluid because this is partially derived from fetal urine.

Prenatal diagnostic studies of propionic and methylmalonic acidemia are done on amniotic fluid. The method for measuring the metabolites in amniotic fluid is stable isotope dilution gas chromatography (discussed later).[10]

Chorionic Villus Sampling

Over the past several years, chorionic villus sampling has become more widespread and popular because of the advantage of an earlier diagnosis. The procedure is usually done between 10 and 12 weeks' gestation and is carried out under ultrasonography by transcervical or transabdominal aspiration. The major complication of CVS is pregnancy loss, which in experienced hands has been shown to be equivalent to that of amniocentesis.[11]

The increasing use of CVS for prenatal diagnosis has stimulated the development of suitable assay procedures for inherited metabolic disorders. A specimen of 10 to 40 mg will provide enough material for most assays. Many assays can be done directly on the homogenate of the biopsy specimen. A culture of the cells from the specimen can also be obtained and the assays done on the cultured cells. A diagnosis using the direct method can be reported within a few days in contrast to assays done on cultured cells, which take at least two to three weeks.

Problems and limitations. The successful use of chorionic villi for prenatal diagnostic tests depends on obtaining specimens of adequate size and uncontaminated by blood or maternal decidua. A careful selection of characteristic villi by microdissection is required to exclude maternal contamination that may lead to a mistaken diagnosis. A typical specimen of 10 to 40 mg provides enough material for the assay of the enzyme under investigation, a reference enzyme, and for measuring protein values.

In twin pregnancies, there is a problem of obtaining specimens from both trophoblasts and interpreting the results. Some investigators recommend doing the study by amniocentesis as a first approach, or in the case of identical results on both CVS specimens, to determine the karyotype and confirm the diagnosis by amniocentesis.[1,12,13]

Enzyme expression. As stated, many enzymes can be assayed directly in the CVS homogenate. Certain enzymes have low levels of expression in uncultured chorionic villi but show greatly increased activity in cultured chorionic villi, thus offering a more reliable approach to the diagnosis.[14]

Enzymes with low activity are α-L-iduronidase (indicating the presence of the Hurler syndrome), neuraminidase (indicating sialidosis), and sphingomyelinase (indicating Niemann-Pick disease). In contrast, glycogenosis type II is more easily and more reliably diagnosed on direct villi because α-glucosidase activity is higher in fresh tissue than in cultured cells.[15]

TABLE 1.—*Metabolic Diseases That Can Be Diagnosed Prenatally*

Disorder	Defect	Inheritance: Autosomal Recessive	Inheritance: Autosomal Dominant	Inheritance: X-Linked	Specimen	Other*
Disorders of Carbohydrate Metabolism						
Galactosemia	Galactose-1-phosphate uridyltransferase	X	--	--	AF cells, CVS	--
Galactosemia	Galactokinase	--	--	--	--	--
Glycogen storage disease						
Type IA von Gierke	Glucose-1-phosphatase	X	--	--	Liver cells	--
Type II Pompe	Acid maltase (α-1,4-glucosidase)	X	--	--	AF cells, CVS	--
Type III Cori	Amylo-1,6-glucosidase	X	--	--	AF cells, CVS	--
Type IV	α-1,4-Glucan: α-1,4-glucan 5-glucosyl-transferase (branching enzyme)	X	--	--	AF cells	--
Disorders of the Urea Cycle						
Argininosuccinic-acidemia	Argininosuccinate lyase	X	--	--	AF cells, AF supernatant, CVS	[^{14}C]Citrulline incorporation
Citrullinemia	Argininosuccinate synthetase	X	--	--	AF cells, AF supernatant, CVS	DNA, AF citrulline
Carbamoyl-phosphate synthetase deficiency	Carbamoyl-phosphate synthetase	X	--	--	Liver cells	DNA
Ornithine carbamoyl phosphate deficiency	Ornithine carbamoyltransferase	--	--	X	Liver cells, CVS	DNA
Hyperargininemia	Arginase	X	--	--	Fetal blood	DNA
Hyperornithinemia						
Type I	Ornithine decarboxylase	X	--	--	--	--
Type II	Ornithine-keto-acid aminotransferase	X	--	--	AF cells	--
Disorders of Mucopolysaccharide (MPS) Metabolism						
MPS I Hurler-Scheie	α-L-Iduronidase	X	--	--	AF cells, AF supernatant, CVS, fetal blood	AF glycosaminoglycan
MPS II Hunter	α-L-Iduronate sulfatase	--	--	X	AF cells, AF supernatant, CVS	AF glycosaminoglycan
Sanfilippo						
MPS III A	Heparan *N*-sulfatase	X	--	--	AF cells, AF supernatant, CVS	--
MPS III B	*N*-Acetyl-α-D-glucosaminidase	X	--	--	AF cells, AF supernatant, CVS	--
MPS III C	Acetyl CoA; α-glucosaminide-*N*-acetyltransferase	X	--	--	AF cells, AF supernatant, CVS	--
MPS III D	*N*-acetyl-α-D-glucosaminide-β-sulfatase	X	--	--	--	--
Morquio						
MPS IV A	*N*-acetylgalactosamine-6-sulfatase	X	--	--	AF cells, AF supernatant, CVS	--
MPS IV B	β-Galactosidase	X	--	--	--	--
MPS VI Maroteaux-Lamy	*N*-acetylgalactosamine-4-sulfatase	X	--	--	AF cells, AF supernatant, CVS	--
MPS VII Sly	β-Glucuronidase	X	--	--	AF cells, CVS	--
Disorders of Steroid Metabolism						
Congenital adrenal hyperplasia type III	21-Hydroxylase	X	--	--	AF supernatant	DNA, AF 17-hydroxyprogesterone
Congenital adrenal hyperplasia IV	11β-Hydroxylase	X	--	--	AF supernatant	AG ss-Deoxycortisol and tetrahydrocortisol
X-linked ichthyosis	Arylsulfatase C	--	--	X	AF cells, CVS	DNA
Disorders of Glycoprotein Metabolism						
α_1-Antitrypsin deficiency	α_1-Antitrypsin	X	--	--	Fetal blood, AF cells, CVS	DNA
Aspartylglucosaminuria	β-Aspartyl-*N*-acetylglucosaminidase	X	--	--	AF cells, CVS	--
Fucosidosis	α-L-Fucosidase	X	--	--	AF cells, CVS	--
Galactosialidosis	α-*N*-Acetylneuraminidase and β-galactosidase	X	--	--	AF cells, CVS	--
Mannosidosis	α-Mannosidase B	X	--	--	AF cells, CVS	--
β-Mannosidosis	β-Mannosidase	X	--	--	AF cells, CVS	--

(continued on next page)

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Disorder	Defect	Inheritance: Autosomal Recessive	Inheritance: Autosomal Dominant	Inheritance: X-Linked	Specimen	Other*
Mucolipidosis I						
Sialidosis	--	X	--	--	AF cells, CVS	--
Infantile, juvenile	(2,3)- or (2,6)-α-*N*-Acetylneuraminidase (glycoprotein)	--	--	--	--	--
Adult	(2,3)- or (2,6)-α-*N*-Acetylneuraminidase	--	--	--	--	--
Mucolipidosis II						
I-Cell disease	UDP-acetylglucosamine-lysosomal-enzyme *N*-acetylglucosamine phosphotransferase	X	--	--	AF cells, CVS	--
Mucolipidosis III						
Pseudo-Hurler polydystrophy	UDP-acetylglucosamine-lysosomal-enzyme *N*-acetylglucosamine phosphotransferase	X	--	--	--	Possible
Disorders of Sphingolipid Metabolism						
Fabry's disease	α-Galactosidase A	--	--	X	AF cells, CVS	DNA
Farber disease	Ceramidase	X	--	--	AFC, CVS	--
Gaucher's disease						
Type 1	Acid β-glucosidase	X	--	--	AFC cells, CVS	--
Type 2	Acid β-glucosidase					
Type 3	Acid β-glucosidase					
GM_1-Gangliosidosis		X		--	AF cells, AF supernatant, CVS	--
Infantile	GM_1-Ganglioside: β-galactosidase					
Juvenile	GM_1-Ganglioside: β-galactosidase					
Adult	GM_1-Ganglioside: β-galactosidase					
GM_2-Gangliosidosis		X	--	--	AF cells, CVS	DNA
Tay-Sachs						
Infantile	β-Hexosaminidase A					
Juvenile	β-Hexosaminidase A					
Adult	β-Hexosaminidase A					
Sandhoff disease		X	--	--	AF cells, CVS	--
Infantile	β-Hexosaminidase A & B					
Juvenile	β-Hexosaminidase A & B					
AB variant	β-Hexosaminidase A activator					
Krabbe's disease	Galactosylceramidase β-galactosidase	X	--	--	AF cells, CVS	--
Mucolipidosis IV	Ganglioside neuraminidase (α-2,8)	X	--	--	AF cells	--
Metachromatic leukodystrophy	Arylsulfatase A or galactocerebroside sulfate sulfatase activator	X	--	--	AF cells, CVS	--
Multiple sulfatase deficiency	Arylsulfatase A, B, C, and steroid sulfatase	X	--	--	AF cells, CVS	--
Niemann-Pick disease		X	--	--	AF cells, CVS	--
Type A	Sphingomyelinase					
Type B	Sphingomyelinase					
Type C	Sphingomyelinase					
Disorders of Amino Acid Metabolism						
Sulfur amino acid metabolism						
Cystinosis	Cystine transport	X	--	--	AF cells, CVS	[^{35}S]Cystine incorporation
Homocystinuria I	Cystathionine β-synthase	X	--	--	AF cells, CVS, fetal blood	--
Homocystinuria II	5,10-Methylenetetrahydrofolate reductase	X	--	--	AF cells	--
Dibasic amino acid metabolism						
Glutaric aciduria I	Glutaryl-CoA dehydrogenase	X	--	--	AF cells, AF supernatant, CVS	--
Glutaric aciduria IIA	Electron transfer flavoprotein	--	--	X	AF cells, AF supernatant	--
Branched-chain amino acid metabolism						
Isovaleric acidemia	Isovaleryl CoA dehydrogenase	X	--	--	AF supernatant	1-[^{14}C]Isovaleric acid
Maple syrup urine disease	Branched-chain keto-acid decarboxylase	X	--	--	AF cells, CVS	3 Hydroxyisovaleric
β-Methylcrotonoylglycinuria	β-Methylcrotonyl-CoA carboxylase	X	--	--	AF cells	--
Disorders of Neutral Lipid Metabolism						
Adrenoleukodystrophy (Schilder's)	Long-chain fatty acid metabolism	--	--	X	AF cells, CVS	DNA
Hyperglycerolemia	Glycerol kinase	--	--	X	AF cells	--
Refsum	Phytanic acid α-hydrolase	X	--	--	AF supernatant, CVS	--
Wolman	Acid lipase	X	--	--	AF cells, CVS	--
Zellweger syndrome	Long-chain fatty acid metabolism	X	--	--	AF cells, CVS	--
Familial hypercholesterolemia type II	Low-density-lipoprotein receptors	--	X	--	AF cells	--

(continued on next page)

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Disorder	Defect	Inheritance: Autosomal Recessive	Inheritance: Autosomal Dominant	Inheritance: X-Linked	Specimen	Other*
Disorders of Propionate and Methylmalonate Metabolism						
Methylmalonic acidemia	Methylmalonyl-CoA mutase, Cob(1)alamin adenosyltransferase deficiency, methylmalonyl-CoA racemase, methylcobalamin methyltransferase	X	--	--	AF cells, AF supernatant, CVS	--
Multiple carboxylase deficiency		X	--	--	AF cells	--
Type I	Holocarboxylase					
Type II	Biotinidase					
Propionic acidemia	Propionyl-CoA carboxylase	X	--	--	AF cells, AF supernatant, CVS	--
Pyruvate carboxylase deficiency	Pyruvate carboxylase	X	--	--	AF cells	--
Hyperphenylalaninemias						
Type I Phenylketonuria	Phenylalanine hydroxylase	X	--	--	Liver cells, AF cells, CVS	DNA
Type II	Dihydropteridine reductase	X	--	--	AF cells	DNA
Other Disorders of Amino Acid Metabolism						
Tyrosinemia type I	Fumarylacetoacetase	X	--	--	AF cells, AF supernatant, CVS	AF succinylacetose
Nonketotic hyperglycinemia	Glycine decarboxylation	X	--	--	AF supernatant, CVS	--
Other Metabolic Disorders						
T-cell immune defect	Nucleoside phosphorylase	X	--	--	Fetal blood	--
Severe combined immunodeficiency	Adenosine deaminase	X	--	--	AF cells, CVS, fetal blood	--
Xeroderma pigmentosum	Defective DNA repair (UV damage)	X	--	--	AF cells, CVS	--
Menkes' syndrome	Intracellular copper accumulation	X	--	--	AF cells, CVS	Copper 64 incorporation
Lesch-Nyhan	Hypoxanthine-guanine phosphoribosyltransferase	--	--	X	AF cells, CVS	Fetal blood
Canavan's disease	Aspartoacylase	X	--	--	AF cells, CVS	--
Hyperoxaluria type I	α-Ketoglutarate:glyoxalate carboligase	X	--	--	Liver cells	--

AF = amniotic fluid, CVS = chorionic villus sampling, UDP = uridine diphosphate

*DNA = diagnosis is made by recombinant DNA techniques.

Fetal Blood Sampling

From 18 weeks' gestation, the prenatal diagnosis of many heritable disorders can be made by fetal blood sampling. Before 1985, fetoscopy was used to visualize the cord directly and obtain the specimens. Since then, successful blood sampling has become an ultrasonographically guided percutaneous procedure.[16] Fetal blood is aspirated through 20- to 25-gauge needles into heparinized syringes and the presence of fetal blood confirmed using a Coulter counter to differentiate fetal from maternal cells on the basis of red cell volume. The fetal loss rate after percutaneous umbilical blood sampling is between 1.5% and 2%.[1]

Fetal blood sampling has been used successfully for the prenatal diagnosis of hemophilia due to deficiencies of factor VIII or IX, von Willebrand's disease, and various hemoglobinopathies including α- and β-thalassemia and sickle cell disease. Other miscellaneous indications include hereditary immune II deficiencies—severe combined immunodeficiency, Chédiak-Higashi syndrome, Wiskott-Aldrich syndrome, chronic granulomatous disease—α_1-antitrypsin deficiency, and abetalipoproteinemia.[1,7,16]

Whereas many of these disorders can be diagnosed by amniocentesis or CVS, fetal blood sampling is useful for the diagnosis of inborn errors of metabolism when a woman presents late in gestation so that results can be available in time to terminate the pregnancy. Fetal blood sampling can also be used in special circumstances when a diagnosis made by CVS or amniocentesis needs confirming.

Fetal Liver Biopsy

A fetal liver biopsy is indicated for the prenatal diagnosis of several liver-specific enzyme defects: ornithine carbamoyltransferase deficiency, von Gierke's glycogen storage disease type IA, carbamoyl-phosphate synthetase I deficiency, and hyperoxaluria type 1 due to α-ketoglutarate:glyoxylate carboligase deficiency (Table 1).[1,15]

Fetal liver biopsies are done with a 16.5-gauge thin-walled needle placed directly below the right costal margin under ultrasonographic guidance. The specimens are centrifuged immediately to separate liver tissue from blood contamination. In the future, as more molecular DNA probes will be available, the indications for this procedure will be fewer. Ornithine carbamoyltransferase de-

ficiency can now be diagnosed in many cases using recombinant DNA technology with a gene-specific probe on chorionic villi or amniocytes.[17]

Fetal Skin Biopsy

Fetal skin biopsies are used for the prenatal diagnosis of metabolic diseases with skin manifestations. Diseases that are usually diagnosed by skin biopsy are epidermolysis bullosa, harlequin ichthyosis, and congenital bullous ichthyosiform erythroderma.[18-20]

Fetal skin biopsies were initially done under fetoscopy. More recently, sampling has been done under ultrasonographic guidance. A trochar is introduced into the uterus under local anesthesia, and a biopsy forceps is passed through it to obtain about 2 mm of skin. The specimens are placed in media and then transferred to appropriate fixative for electron microscopy and light microscopy. The worldwide experience suggests a 3% to 4% spontaneous abortion rate after fetal skin biopsy.[1]

When a known enzyme is involved, chorionic villi or amniocytes can be used for the diagnosis of the specific disease, such as in X-linked ichthyosis (arylsulfatase C deficiency), Refsum disease (phytanic acid storage disease), and Fabry's disease (α-galactosidase A deficiency).

Prenatal Diagnosis of Inborn Errors of Metabolism

Enzyme Analysis

The simplest and most direct way to demonstrate an enzyme defect is to assay the enzymatic activity in a crude tissue homogenate using a specific substrate under optimal conditions. When conventional biochemical techniques are used in prenatal diagnosis, 10^5 to 10^7 amniotic fluid cells are required; this usually requires periods of cultivation of three to six weeks. Microtechniques have been developed that enable biochemical analysis of few (10 to 1,000) cultured amniotic cells. These methods use a small number of cultured cells following the cleavage of fluorescent or fluorogenic natural substrate.[21]

The substrates used for many enzymes are synthetic compounds that are used in a fluorimetric or colorimetric assay system. In some assays, natural substrates are used. The enzymatic activity is measured and related to the protein concentration.[22] Chromatographic and electrophoretic methods are sometimes used for delineating different enzymes.[23] Immunologic methods can be used to investigate enzymatic defects, usually with monoclonal or specific antibodies. With these methods, enzymes that use the same substrate or demonstrate the presence or absence of an enzyme by immunochemical technique can be separated.[24]

Molecular Analysis

Analysis of DNA has several advantages. First, the fetal specimens can be obtained by CVS in the first trimester or by amniocentesis in midtrimester. Those techniques are much safer and easier to master than, for example, more invasive techniques such as fetal liver biopsy or fetal blood sampling. Second, DNA analysis permits the diagnosis of diseases in which the gene product is unknown, as in spinal muscular atrophy. Third, DNA analysis does not require gene activity, and the diagnostic studies can be done on any tissue (chorionic villi, amniocytes) unlike, for example, ornithine carbamoyltransferase deficiency that in the past required fetal liver biopsy.[17,25] Table 2 lists many of the metabolic disorders that have been diagnosed by DNA analysis.

TABLE 2.—*Metabolic Disorders Identified by DNA Analysis*

Disease	*Method*
Cystic fibrosis	Direct, RFLP
Ornithine carbamoyltransferase deficiency	RFLP
Phenylketonuria	RFLP
Carbamoyl-phosphate synthetase deficiency	RFLP
Glycerol kinase deficiency	Direct
Congenital adrenal hyperplasia	Direct
X-linked adrenoleukodystrophy	Direct, RFLP
Lesch-Nyhan syndrome	Direct, RFLP
Fabry's disease	Direct, RFLP
Tay-Sachs disease	Direct, RFLP
X-linked ichthyosis	RFLP
Familial hypercholesterolemia	Direct, RFLP
Duchenne-type muscular dystrophy	Direct, RFLP
Myotonic dystrophy	RFLP
Hemophilia A	RFLP
Hemophilia B	RFLP
Sickle cell anemia	Direct
α-Thalassemia	Direct
β-Thalassemia	Direct, RFLP
Hereditary amyloidosis	Direct
α_1-Antitrypsin deficiency	Direct, RFLP

RFLP = restriction fragment length polymorphism

Direct Analysis

Direct detection is used in cases in which a mutation alters an endonuclease restriction site (sickle cell anemia), a mutation results in gene deletion (α-thalassemia, Duchenne muscular dystrophy), or there is a known mutation for which there is a DNA probe for the mutation (β-thalassemia, α_1-antitrypsin deficiency).

Indirect Analysis

Indirect techniques use restriction fragment length polymorphisms (RFLPs), which are normal, inherited sequence variations in DNA. They are unrelated to genetic defects, but if they occur in extremely close chromosomal proximity to a genetic defect (linkage), they are used as markers to track the inheritance of the mutant gene.

Methods using RFLPs have proved useful for the prenatal diagnosis of metabolic disorders. The major limitations in using them include the need to establish the linkage status of polymorphisms and the affected gene in each family, the need for informative polymorphisms, and genetic recombination.

Advances in the application of DNA analysis, and in particular the new techniques of gene amplification by PCR, have enabled the detection of an increasing number

of mutations that are diagnostic for inherited diseases. With PCR techniques, it is possible to use small amounts of genomic DNA for analysis. Adequate DNA can be directly extracted from amniotic fluid (10 ml) from 8 weeks' gestation onward, and these specimens are suitable for prenatal diagnosis using PCR.[26]

Quantitative Studies After Incorporating Radioisotopes

The activity of an enzyme may be measured indirectly by the use or incorporation of a radioactively labeled precursor in living chorionic villi or cultured amniotic cells. This procedure has been useful for the diagnosis of several metabolic disorders.

The approach of measuring the incorporated radioactivity by living cells has been used for the prenatal diagnosis of copper accumulation in Menkes' disease,[27] by using copper chloride Cu 66, argininosuccinic acid synthetase, and argininosuccinase deficiency by using citrulline labeled with carbon 14. The prenatal monitoring of inborn errors of propionate, methylmalonate, isovalerate, and cobalamin metabolism has been successful using radioisotope incorporation studies.

These radiometric methods can be performed in microassays. [^{14}C]Oxygen liberation is measured after the incubation of cells with 1-[^{14}C]keto acid for the diagnosis of maple syrup urine disease, or for the diagnosis of medium-chain acylcoenzyme A dehydrogenase deficiency.[28]

The prenatal diagnosis of cystinosis has been achieved by the expeditious analysis of the cystine content in fresh chorionic villi. Because free cystine is rapidly lost even with frozen storage, a more reliable approach to the diagnosis of cystinosis is to culture villi in cystine labeled with sulfur 35 and to measure the retention of the labeled metabolite.[29]

Stable Isotope Dilution Gas Chromatography-Mass Spectrometry

The method of choice for measuring metabolites in amniotic fluid is stable isotope dilution gas chromatography with mass spectrometry. In this procedure, an analogue of the compound to be detected, labeled with stable isotope, is included as a carrier and as an internal standard, preventing inaccuracy due to loss by absorption of the compound being analyzed. This method provides high sensitivity and specificity, even with low concentrations of metabolites. Methylmalonic acidemia, propionic acidemia, glutaric aciduria type II, tyrosinemia type I, isovaleric acidemia, and galactosemia can be detected with this method of cell-free amniotic fluid.[10,30]

Confirming the Diagnosis

When the prediction is made of an abnormal fetus and terminating the pregnancy is contemplated, studies should be done to confirm the diagnosis. A detailed histologic examination of the abortus and the collection and examination of specimens for metabolic studies are essential.

When prenatal diagnostic studies have indicated an unaffected fetus or a carrier status, adequate assessment and follow-up are required to confirm that the infant is clinically unaffected. If the parents have decided to carry an affected fetus to term, preparations should be made to confirm the diagnosis and institute appropriate therapeutic intervention immediately after delivery.

Specimens for metabolic studies can be obtained from different tissues: cord blood, placental tissue, amnion, urine, liver, skin. Specimens should be refrigerated or frozen, preferably at −70°C (liver, skin). Those specimens can be analyzed for organic and amino acids mucopolysaccharidoses and enzymatic assays. Fresh tissue for DNA extraction and analysis should be frozen; a good source is the placenta. Tissue for electron-microscopic studies should be obtained rapidly and placed in cold fixative. Consulting with the laboratory professionals who do the test can be helpful.

The results of the confirmatory studies on both affected fetuses and unaffected newborns should be transmitted to the physician and parents as soon as possible.

Summary

As can be seen from the foregoing discussion and the tables, a wide range of metabolic disorders have been diagnosed prenatally in fetuses. Several principles are important to remember when approaching a possible prenatal diagnosis. The most critical is to confirm the diagnosis of the disorder for which the couple is at risk. Only with this information can a specific analysis be undertaken. Frequently this may involve the testing of other family members to confirm the heterozygous state or to establish linkage in molecular studies.

Another principle is to show that the specific enzyme or metabolite being measured is present in the fetal tissue type and at the gestational age being studied. It must also be shown that there is an abnormality that can be measured in the disease state.

The final principle is to use the least invasive procedure possible to obtain the diagnosis. For example, as mentioned above, ornithine carbamoyltransferase deficiency can be diagnosed by both fetal liver biopsy and molecular studies in informative couples. Obtaining a fetal specimen by amniocentesis or CVS is clearly less invasive than doing a fetal liver biopsy.

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Clinical Teratology

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The field of teratology has become increasingly important in preventive medicine programs. By avoiding specific teratogenic agents, many birth defects can be prevented. In this review we will summarize the currently documented teratogenic agents in humans.

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Of the various birth defects, 5% to 10% have environmental causes that include drugs, 50% to 60% have an unknown cause, 0.5% are due to chromosomal aberrations, and the remaining 25% to 30% are due to genetic factors.[1,2] Because of the importance of environmental factors in the etiology and prevention of congenital anomalies, much effort has gone into finding environmental teratogens and understanding their mechanisms of action. Much of our understanding of teratogenic mechanisms comes from work on animals, but care must be taken when applying these results to humans. In many cases, teratogenic exposures in one animal may not be harmful in even another strain of the same animal. Moreover, known human teratogens are not always teratogenic in animals.

Several factors are important in evaluating a possible teratogen. The first is the timing of the exposure. Because of the constant changes in development, the fetus may be sensitive (vulnerable) to teratogenic insults only at specific times. At different stages of development, the same teratogen may result in death or have no effect at all. The next factor is the dose of a drug. Usually a minimum "threshold" exists below which little effect is seen. The last ingredient is the pharmacokinetics of an agent. Individual biochemical pathways of both fetus and mother are extremely important. Identical exposures may have different results depending on enzyme levels of the mother or fetus. All of the above can increase the teratogenic potential of any given exposure. A combination of teratogenic factors may also increase the risk to the embryo.

The Effects of Drugs on the Human Fetus

Several compounds and drugs may be responsible for congenital defects in human offspring when administered during pregnancy. Evidence for the teratogenic action of these drugs has accumulated from human experience and from studies of animals.[2] In addition to the pharmaceutic effects of drugs on a pregnant woman and her fetus, drugs may also affect fertility and general reproductive performance. The adverse effects of drugs and chemicals are usually manifested at birth. The initial manifestations of central nervous system defects occurring in utero often present themselves during infancy or later. This may lead to a relatively late recognition of the teratogenic effects of drugs.[3] Various experimental models exist for teratogenicity testing of chemicals—in vivo animal models as well as various in vitro systems. These include embryo cultures, limb bud culture, cultures of specimens of isolated fetal organs (such as long bones), and studies of cultured embryonic cells. Each one of these systems has specific advantages and disadvantages.[4-8] The most widely used animals for the study of drugs are rodents—mice, rats, and rabbits. Many laboratories have also introduced primate models for teratogenic studies, which have an obvious advantage over other mammals. An important disadvantage is the interspecies differences in pharmacokinetics and toxicity. This is best exemplified by the teratogenic effects of thalidomide that occur in humans but not in several animal models or of salicylates and glucocorticoids that are teratogenic in mice and rats but not in humans.[5-8] Despite these difficulties, in vivo studies are still used for teratogenicity testing of drugs. It is advised that they be done in at least two animal species (preferably including primates). The drugs are administered in several dosage levels at different times during gestation, specifically including the period of organogenesis.[9]

Teratogenic Agents in Humans

Chemical Agents

The list of drugs or chemicals that have been implicated or proved to be teratogenic in humans includes anticonvulsants, radioactive materials, heavy metals, alcohol, and various other drugs. Because of the continuous flow of information, the list of teratogenic drugs is constantly being altered as new evidence accumulates.[10-12]

Folic acid antagonists. The embryolethal effect of folic acid antagonists such as methotrexate or aminop-

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ABBREVIATIONS USED IN TEXT

CMV = cytomegalovirus
DES = diethylstilbestrol
Ig = immunoglobulin

terin on animals in the laboratory was the basis for their use as abortifacients in human pregnancies.[13] Some of these subsequent abortions failed, and 23% of surviving embryos were malformed. The type of malformations varied, depending on the time of exposure to the drug. Aminopterin has been shown to cause growth retardation, skeletal defects, and hydrocephaly.[14] Another folic acid antagonist, methotrexate, is used in cancer chemotherapy and in treating psoriasis. Because of the widespread use of methotrexate, it may inadvertently be used in early undiagnosed human pregnancy. Thus, its use should be carefully monitored.

Alcohol (ethanol). Following the description by Jones and co-workers of the fetal alcohol syndrome in 32% of exposed infants, numerous other studies have appeared.[15] Mulvihill and Yeager reported that of 23 offspring exposed to large amounts of alcohol in utero from the Perinatal Collaborative Project, 6 (26%) displayed the fetal alcohol syndrome.[16] This includes prenatal and postnatal growth retardation, mental deficiency, small head size, and minor anomalies of the face, eyes, heart, joints, and external genitalia. A similar malformation rate was reported by Lemoine and associates.[17] Mental retardation is the most serious effect, and a review of clinical and animal studies indicates that the fetal alcohol syndrome may be one of the most commonly recognized causes of mental retardation in some countries.[18] The teratogenicity of alcohol is associated with the dose and the time of exposure, although the exact dosage and susceptible period have not yet been determined. Folic acid deficiency may be an important factor in teratogenicity, as alcohol interferes with folate metabolism.[19] It is uncertain whether binge drinking of ethanol is also teratogenic or may affect the neurobehavioral development of the children exposed in utero.[20]

Sodium warfarin. The treatment of a woman with sodium warfarin during pregnancy has been associated with a specific syndrome of congenital anomalies.[21] The major defect in the embryo is nasal hypoplasia and epiphyseal calcification of the long bones and vertebrae. Although Warkany among others cited a number of cases with central nervous system defects (usually including microcephaly and optic atrophy), more recent reports of acenocoumarol treatment after the 12th week of gestation have not supported this finding. In light of the existence of only a few reported cases of anomalies following second-trimester exposure to warfarin, the use of this drug from the second trimester and thereafter is considered by several investigators to be safe.[22,23] The preferable anticoagulant used during pregnancy seems to be heparin, including low-molecular-weight heparin, which does not pass through the placenta and is not teratogenic.[10,11]

Diethylstilbestrol. In 1971 Herbst and co-workers reported adenocarcinoma of the vagina in seven of eight young women with exposure to the synthetic estrogen diethylstilbestrol (DES) in utero during the first three months of gestation.[24] According to the DES registry, it is estimated that the risk of clear cell adenocarcinoma of the vagina and cervix developing in DES-exposed women younger than 24 years is between 0.14 and 1.4 per 1,000.[25] The National Cooperative Diethylstilbestrol Adenosis Project, which included 3,339 women with DES exposure, found that the incidence of vaginal epithelial changes was related to the time of exposure in gestation and the dose of the drug.[26] Of 134 male fetuses with exposure in utero, 27% had genital lesions and 29% had abnormalities in the spermatozoa; none showed any signs of malignancy.[27] Following these reports, the use of synthetic estrogens during pregnancy was discontinued.

Thalidomide. The reports in the 1960s of an increase in the frequency of limb defects after in utero exposure to thalidomide showed this sedative to be a potent teratogen in humans.[28] The drug is teratogenic if ingested in sufficient dosage from the third to the sixth week after conception. It produces characteristic defects of limbs, heart, and, less often, other organs. These malformations were well correlated with the time of exposure. It is estimated that 20% of infants with in utero exposure to thalidomide during the susceptible period were born with malformations. Even a single dose has been shown to cause defects.[29]

Chemotherapeutic agents. These drugs have various cellular effects and may also react with various sites in the DNA molecule.[19] Many of them are also cytotoxic and highly teratogenic as shown in studies of animals. Because of their potent teratogenic effects in animals, their use in pregnant women has been limited; therefore, almost nothing is known about their human teratogenic potential. Several case reports, however, emphasize the highly embryotoxic and teratogenic effects of many of these drugs.[11]

Alkylating agents represent the largest class of mutagenic chemotherapeutic agents that react with various sites in the DNA molecule. These compounds may alter the DNA or may induce transitional mutation as a result of erroneous pairing.[19] Other antimitotic drugs include vinblastine, vincristine, dactinomycin, and cytarabine. An increased incidence of spontaneous abortion has been noted following the use of these drugs.[30]

Vitamin A and retinoids. Both a deficiency and an excess of vitamin A have been proved teratogenic in animals, causing ocular, central nervous system, skeletal, and other anomalies. Several cases have been reported of congenital malformation in humans after excess vitamin A exposure.[31] Isotretinoin (Accutane, or 13-*cis*-retinoic acid), a drug used for the treatment of severe acne, has been shown to be teratogenic in humans when taken in therapeutic doses. Lammer and associates prospectively identified 57 women with exposure in their first trimester. They found a 23% risk for major malformation after first-trimester exposure to isotretinoin. These malformations involved craniofacial, cardiac, thymic, and brain develop-

ment.[32] The half-life of isotretinoin is short, so that discontinuing the drug before pregnancy should eliminate the teratogenic potential. Etretinate, however, a vitamin A cogener used to treat severe psoriasis, has a much longer half-life and should be discontinued at least a year before pregnancy.

Anticonvulsants. Since the early report by Müller-Küppers on the teratogenic effects of mephenytoin, much information has accumulated in the literature on the association between anticonvulsant drugs, maternal epilepsy, and congenital malformations.[33] Speidel and Meadow in 1972 observed that the incidence of congenital malformations is increased in the offspring of epileptic women, some of the increase is apparently due to the medication used by these women for their epilepsy, and the children of treated women display a characteristic pattern of anomalies, but one that varies in severity.[34] The effect of this class of drugs can be described best when examining each drug individually.

- *Trimethadione, paramethadione:* In 1970 German and colleagues reported the effects of in utero exposure of trimethadione or paramethadione (a homologue of trimethadione) in four women.[35] They described a pattern of anomalies among the offspring that was later called the fetal trimethadione syndrome. Numerous subsequent cases were reported with similar findings, consisting of characteristic craniofacial anomalies, delayed growth and psychomotor development, clefting, congenital heart defects, and an increased rate of fetal and infant death.[36] This drug was originally used for the treatment of petit mal epilepsy, but has been replaced by ethosuximide and valproate. Because of their teratogenic effects, trimethadione and paramethadione should not be used by women during childbearing years.
- *Phenytoin (Dilantin), hydantoin:* Phenytoin passes the placenta. Similar concentrations have been measured in maternal and umbilical cord plasma at delivery, indicating that an equilibrium state is attained with long-term administration.[37] Although some prospective studies found no effect of hydantoin on the rate of malformations, many others have found an association between the use of the drug and a definite pattern of anomalies, the "fetal hydantoin syndrome." These include cleft lip and palate, heart disease, and microcephaly.[38] In addition, distal digital hypoplasia appears to be a specific marker in 18% of infants born after in utero exposure to hydantoin.[39] Infants of epileptic women with exposure to phenytoin in utero have had at least twice the expected rate of congenital malformations. Hanson and Smith concluded that as many as 11% of exposed infants have the fetal hydantoin syndrome and three times as many have impaired performance or morphogenesis, including impaired growth.[40] Epoxide hydrolase deficiency in the fetus has recently been associated with those fetuses that manifest the fetal hydantoin syndrome.[41] Epoxide hydrolase levels may be measured in cultures of both parental fibroblasts and fetal amniocytes.
- *Valproic acid:* Valproic acid and its sodium salt, sodium valproate, are anticonvulsants used in treating a number of seizure disorders. Several case reports have associated the use of these drugs with a variety of malformations. DiLiberti and co-workers introduced the term "fetal valproate syndrome," which consists of typical craniofacial anomalies, including epicanthal folds, flat nasal bridge, and changes in the shape of the mouth.[42] Some infants have also had limb anomalies. An increased incidence of neural tube defects of about 1% has been reported after first-trimester exposure to valproic acid.[43] Recent epidemiologic studies suggest a somewhat higher incidence of neural tube defects.[44]
- *Carbamazepine:* Previously considered to be relatively safe during pregnancy, carbamazepine is now thought to have teratogenic potential. The incidence of anomalies in one report among children born to epileptic women taking carbamazepine was two to three times higher than in the general population.[45] The existence of a fetal carbamazepine syndrome manifested by growth and developmental delay and minor craniofacial and other anomalies has been suggested by several investigators.[46] An increased risk of neural tube defects has also been reported.[47] A combination of carbamazepine and other anticonvulsants was found to have increased teratogenic potential.[45]
- *Barbiturates:* In most reports, barbiturates have not been considered teratogenic. Most studies have reported no increase in the incidence of malformations among offspring of epileptic women with exposure to phenobarbital during pregnancy. There has also been no indication of an increase in malformations when the drug was used for other than epilepsy.[48,49(p343)] A higher incidence of minor malformations was recently described among infants of epileptic women treated with phenobarbitone.[50] Mysoline has a pharmaceutic effect equal to that of barbiturates.[19] Although women with epilepsy must be treated during their pregnancy, the administration of anticonvulsants with a high teratogenic potential should be avoided. It is therefore advisable to change antiepileptic regimens to weaker teratogens such as barbiturates, mysoline, and benzodiazepines before pregnancy to evaluate the treatment effectiveness.

Radioactive iodine. Iodine 1 131 is in common use in nuclear medicine. This isotope can damage or ablate the developing thyroid in human fetuses. A number of cases of congenital hypothyroidism have been reported after fetal exposure to ^{131}I in utero.[51] Women who have been treated with high doses before conception have not had an increase in malformations in their subsequent pregnancies.[52] Inorganic iodides can easily cross the placental barrier, and 3% to 4% of the maternal dose crosses the placenta and is taken up by the fetus. The fetal thyroid is able to concentrate iodide by the tenth gestational week and will continue to do so until the end of gestation. Moreover, the fetal thyroid has a greater affinity for iodide than does the maternal thyroid.[53] Labeled compounds, which do not easily cross the placenta, usually release substantial amounts of iodide. Therefore, most labeled iodide compounds release some iodine that will eventually be taken up by the fetus.[10-12] Although tracer doses of ^{131}I

have not been reported to cause malformations in the fetus, if ^{131}I must be given, it is advisable to administer it before the seventh gestational week.

Selenium. Pancreatic screening with selenomethionine Se 75 can be deleterious in pregnant women as 1.4% to 1.5% of the dose crosses the placenta after intravenous administration to the mother. The fetus concentrates this material in the liver, gut, and kidneys. Because of its long biologic half-life, it may be dangerous to the fetal pancreas.[54]

Lead. There has been concern for many years over the effects of lead on the developing fetus. One study indicated a twofold to threefold increase in the rate of spontaneous abortion in women with exposure to lead during pregnancy, mainly as a result of placental hemorrhage.[55] Recent reports have shown an association between increased levels of lead and developmental delay.[56]

Organic mercury compounds. Alkyl mercury compounds have proved to adversely affect the development of the human fetus, as was shown by the effect of methyl mercury at Minamata Bay in Japan. An epidemic of neurologic symptoms, due to the degeneration of the cerebral and cerebellar cortices, and of microcephaly was traced to eating mercury-contaminated fish.[57] Other cases were also reported in the United States and Iraq.[58,59] Even at concentrations that do not produce symptoms in the mother, methyl mercury may affect the fetus because the fetus appears to have a greater affinity to mercury than the mother. A higher concentration of mercury occurs in umbilical cord erythrocytes than in maternal blood, and the level of mercury in the fetal brain appears to be twice that in the maternal brain.[60]

Carbon monoxide. Carbon monoxide produces anemic hypoxia by inactivating the oxygen-carrying capacity of the hemoglobin molecule. A number of experiments indicate its teratogenicity in animals, but little is known about its teratogenic potential in humans. In humans, the fetal carboxyhemoglobin concentration depends on the maternal carboxyhemoglobin concentration and endogenous carbon monoxide production. At steady state, the fetal carboxyhemoglobin concentration is 10 to 15 times greater than maternal levels. Carbon monoxide uptake and release are slower in the fetus than in the mother. In addition, pregnant women are more sensitive to the effects of carbon monoxide than nonpregnant women.[61] Several reports of carbon monoxide intoxication of pregnant women have described fetal mortality, with surviving offspring showing physical abnormalities and neuromotor impairment.[62] There seems to be no study in humans to show the effect of moderate concentrations of the gas. A possible indication of the effect of carbon monoxide may be that of maternal smoking on the fetus. This results in increased blood carboxyhemoglobin levels, a decrease in the mean birth weight, and possible impaired psychomotor development.[63]

Amphetamines. Amphetamines have been shown to be teratogenic in animals. The frequency of congenital anomalies in humans, however, was no greater than expected among children of 367 women who took dextroamphetamine during the first four months of pregnancy.[49(pp346-355,459,491)] Reports of sporadic cases of an increased incidence of congenital heart defects and biliary atresia have been associated with the use of amphetamines during early pregnancy, possibly indicating a low level of teratogenicity in humans.[64] Eriksson and associates studied the development at age 8 years of 71 children born to amphetamine-addicted women.[65] Their functional cognitive level was normal as was their physical health including growth. An increased incidence of aggressive behavior was observed among these children, however.[65] One study has reported an increase in the incidence of neural tube defects when anorectics containing amphetamines were used during organogenesis, and there was a concomitant notable weight loss.[66] To date, the evidence for any teratogenicity remains inconclusive.

Iodides. Extended ingestion of iodine-containing medications during pregnancy can lead to thyroid enlargement. These congenital goiters are due to fetal thyroid inhibition with secondary compensatory hypertrophy. In some cases the thyroid enlargement can lead to tracheal compression and asphyxia in the newborn.[67] Burrow reported that 80% of the mothers of infants with congenital goiters received iodine and propylthiouracil.[68] The reported doses of iodine that caused neonatal goiters ranged from 18 to 2,010 mg daily.[69] Because of the frequency of congenital goiters, the long-term use of iodine preparations should be avoided during pregnancy.

Lithium carbonate. The teratogenic potential of lithium carbonate in humans, used in the treatment of manic-depressive illnesses, is inconclusive. The original registry of pregnancies with exposure to lithium reported a malformation rate of 7.6%, with several cases of Ebstein's anomaly.[70] Recent prospective studies have not confirmed these findings. The studies found no significant increase in the percentage of congenital defects after in utero exposure to lithium. One case of Ebstein's anomaly, however, suggested a possible relation between lithium and this defect.[71]

Antibiotics. Most antibiotics—penicillin, sulfonamides—have no known teratogenic effects in humans. Aminoglycosides, which are known to have a nephrotoxic and ototoxic effect, may similarly transplacentally affect the human fetus.[72] Tetracyclines have known teratogenic effects in animals, such as cleft lip and palate, enamel hypoplasia, and other malformations. In humans, a discoloration of tooth enamel and enamel hypoplasia have been reported.[73] The use of the combination of sulfamethoxazole and trimethoprim, a folic acid antagonist, is usually contraindicated during pregnancy because of the theoretical possibility that trimethoprim will induce folic acid deficiency. Large controlled human studies have not substantiated this theoretical risk.[74(p621)]

Cocaine. Cocaine use during pregnancy is known to cause abruptio placentae and various antenatal and postnatal complications including prematurity, intrauterine growth retardation, cerebral hemorrhage, and sudden infant death.[75,76] Although many studies have shown an increased rate of congenital anomalies, they must be inter-

preted with caution because there is no specific syndrome attributed to cocaine exposure. There does seem to be an increased incidence of genitourinary system anomalies and of disruptive brain anomalies.[75,77] Relatively few data exist on the subsequent growth and development of children born to women who have used cocaine during pregnancy, and therefore no conclusive data exist on the later intellectual function of these children.

Heroin. Epidemiologic studies of malformations in children of heroin-addicted women have not shown an increased rate of anomalies attributable to heroin use.[76,78] Intrauterine growth retardation, prematurity, perinatal death, and a variety of perinatal complications have been noted, as well as a high rate of withdrawal symptoms. Initial follow-up studies looking at the psychomotor development of children born to heroin-addicted women found developmental delay, hyperactivity, inattention, and behavioral problems.[76] More recent studies suggest that these developmental abnormalities are environmentally related because they were not found among children born to heroin-addicted women and raised by "normal" foster families.[78]

Physical Factors

Radiation. High-energy radiation (γ-rays, x-rays) is a physical factor that may exert a number of effects on the embryo: teratogenic, carcinogenic, or mutagenic. It is important to note that any of the deleterious effects of radiation are produced at threshold doses, with radiation at lower doses not producing any significant effects.[79] Before the blastocyst stage, the embryo is apparently most sensitive to the lethal effects of radiation and not to its teratogenic effects. During early organogenesis, radiation may be teratogenic and cause growth retardation, although the embryo may recover from the growth retardation in the postpartum period. Early in the fetal period, the major damage is to the central nervous system. The fetus may have permanent cell depletion of different tissues if exposed to high levels of radiation. There may be a number of mechanisms for the effect of radiation, including cell death, the inhibition of cell migration, or chromosomal aberrations.

The teratogenic effect of radiation on the human embryo was first described by Goldstein and Murphy in a group of pregnant women undergoing therapeutic irradiation.[80] When the radiation dose was 0.5 to 3 Gy (50 to 300 rad), the infants had a higher incidence of microcephaly, mental retardation, and various anomalies. There was also a higher incidence of fetal and infant mortality.[81] Only a direct dose to the fetus of 0.05 to 0.1 Gy (5 to 10 rad) and above constitutes a real risk to the fetus.[82] In most cases of diagnostic irradiation, the woman receives exposure to doses that are much below this threshold. When a pregnant woman receives radiation in the abdominal region, about 50% of the dose reaches the fetus. The amount of fetal irradiation is lower if the area of x-radiation is farther away from the abdominal region. After a skull x-ray film, the embryo would be exposed to only a negligible amount of radiation. Abdominal computed tomographic scans and fluoroscopy might expose a fetus to radiation that is close to the threshold. The human fetal brain appears to be most susceptible during weeks 8 to 15 of gestation.[83] There have been many studies concerning in utero exposure to radiation and the risk of leukemia and other cancers. Although several studies claim that in utero exposure of 0.01 to 0.02 Gy (1 to 2 rad) increases the risk of childhood malignancy by a factor of 1.3 to 2 over the natural incidence, many others have disagreed with these findings.[84-87] Radioactive materials with γ-radiation, such as cobalt and radium, produce exposures similar to that of x-rays. Materials with α- and β-radiation, because of their short range, are a risk to a fetus only when they pass the placental barrier after entering the maternal bloodstream.[10]

Intrauterine Infections

The incidence of intrauterine infections ranges between 3% and 15%. In the past, the most common intrauterine infection with a teratogenic agent was rubella.[88] Today, because of effective immunization programs against rubella, the most common infection is apparently that caused by cytomegalovirus (CMV). Although the exact number of infants born with intrauterine infections is unknown, it is well accepted that 1% to 2% of newborn infants have congenital CMV, and 15% to 20% of these infants will have long-term sequelae of this disease.[89] Moreover, Altshuler and associates found that about 6% of term placentas show histologic evidence of intrauterine infection.[90] In infants who are small for their gestational age, the incidence of intrauterine infections seems to be higher.

Intrauterine infections with long-term fetal sequelae may be viral, parasitic, and bacterial. The more common intrauterine infections have a viral cause. There are two modes of transmission of the infection to the fetus: hematogenous spread from the maternal circulation through the placental barrier and then to the fetal circulation, and ascending infection from the mother through the fetal membranes with direct contamination of the amniotic fluid. Villitis and deciduitis are common abnormalities in cases of hematogenous spread, whereas chorioamnionitis and funisitis are found in cases of ascending infection.[90,91] Cases of intrauterine infections are initially evaluated by measuring the serum levels of maternal specific antibodies during pregnancy. This is carried out whenever there are any clinical signs in the pregnant woman. In the more common intrauterine infections such as CMV and toxoplasmosis, only rarely are distinct clinical manifestations seen in the mother. Moreover, a maternal rise in levels of specific antibody is diagnostic for maternal and not necessarily for fetal infection. To diagnose fetal infection, the infective agent should be identified in the amniotic fluid by culture or by the presence of viral DNA or RNA demonstrated by polymerase chain reaction method on amniotic fluid cells, or specific immunoglobulin (Ig) M found in fetal blood following percutaneous umbilical blood sampling. This last test should be done after 22 weeks' gestation, as false-negative re-

sults have been reported earlier than this.[92] At birth, cord blood IgM isolation of the agent from the newborn or specific clinical findings (or both) are the most relevant diagnostic tools. In addition, a microscopic examination of a specimen of the placenta or fetal membranes may help in the diagnosis of intrauterine infection. Unfortunately, many of the inflammatory lesions—villitis, deciduitis, and chorioamnionitis—are not specific to any single infection.[91] Specific placental lesions have been described in infections with CMV, syphilis, herpesvirus, Epstein-Barr virus, and rubella.[88,92,93]

Immunization with attenuated live viruses during pregnancy does not seem to have any adverse effect on the fetus. This includes poliovaccine, measles, mumps, hepatitis, and even rubella.[88,94] Despite the fact that there is no report of increased congenital anomalies with these immunizations, it is advisable to use them only when there is a substantial risk of maternal infection. Although the attenuated rubella virus has been found to reach the fetus, no cases of congenital rubella have been described following rubella vaccination during pregnancy.[95] Despite this, it is not advisable to immunize against rubella during pregnancy.

Rubella. The congenital rubella syndrome, originally described by Gregg in 1941, consisted of heart disease (most often patent ductus arteriosus or peripheral pulmonic stenosis), deafness, and cataracts.[96] The syndrome now includes intrauterine growth retardation, encephalitis, radiographic changes in the long bones, and continued infection in the infant for months after birth. After birth, findings of hepatosplenomegaly, obstructive jaundice, and thrombocytopenic purpura are common. Long-term sequelae include mental retardation, neurologic deficits, and behavioral abnormalities. Children who are unaffected at birth may later have deterioration of hearing or mental functions, as the infections tend to be chronic. In addition, older persons with exposure to intrauterine infection may have late sequelae such as diabetes mellitus or progressive rubella panencephalitis.[92,96-98]

Cytomegalovirus. Cytomegalovirus produces a clinical syndrome (cytomegalic inclusion disease) consisting of intrauterine growth retardation and microcephaly. In addition, there may be chorioretinitis, seizures, blindness, and optic atrophy. In the neonatal period, hepatosplenomegaly, jaundice, and thrombocytopenia may develop. Within the first three years, 10% to 25% of infants with congenital CMV infection who are initially asymptomatic may have sensorineural hearing loss, chorioretinitis, neurologic defects, and dental defects. Various degrees of mental retardation are present.[88,99,100]

Varicella-zoster virus. An unusual array of abnormalities has been described in infants with in utero exposure to varicella. The features include cicatricial skin lesions, fetal growth retardation, limb hypoplasia, and brain and eye defects. Cerebral, cortical, and cerebellar atrophy, seizures, developmental delay, and nerve palsies are common. Many of the affected newborns die in infancy. Only about 25 cases of infants with these abnormalities have been reported.[101,102]

Epstein-Barr virus. Most studies have not proved any association between Epstein-Barr virus infection in utero and an increased incidence of malformations. Cases of prenatal Epstein-Barr virus infection and infants born with malformations have been reported, however. These include three infants with cataracts, two infants with congenital heart defects, and two infants with diffuse myocarditis. In addition, another cohort study reported on a statistical increase in prematurity, growth retardation, and fetal death. The added risk of malformations in an infant after prenatal exposure to Epstein-Barr virus appears to be minimal, however.[93,103,104]

Parvovirus B19 (fifth disease). In utero exposure to parvovirus B19 has not as yet been proved to cause an increase in malformations. Several cases of fetal hydrops after first- or second-trimester transplacental infection have been reported. Microscopic examination showed severe aplastic anemia. In addition, there have been at least three cases of ocular malformations.[105,106]

Toxoplasmosis. The clinical features of congenital toxoplasmosis in severely infected infants include encephalitis, hydrocephalus, intracranial calcifications, chorioretinitis, erythroblastosis, anemia, jaundice, hepatosplenomegaly, glomerulitis, myocarditis, and myositis, as well as increased neonatal mortality. Central nervous system damage is found in almost all cases. Manifestations of the disease, which may appear later, include seizures, mental retardation, cerebral palsy, deafness, and blindness. The clinical features of congenital toxoplasmosis were first described in 1923.[88,107,108]

Syphilis. In utero exposure to syphilis may result in congenital malformations, prematurity, or stillbirth. The characteristic clinical findings in infants with congenital syphilis include hepatosplenomegaly, osteochondritis or periostitis, jaundice, petechiae or purpuric skin lesions, lymphadenopathy, hydrops, edema, ascites, rhinitis, pneumonia alba, myocarditis, nephrosis, and pseudoparalysis.[109]

Nutritional Deficiency

In humans, nutritional deficiency has been found to be associated with lower birth weight,[110] but not with any increase in specific congenital anomalies. Folic acid deficiency seems universally to be teratogenic in most animal species, including humans.[11,12] Drugs such as methothrexate and aminopterin, which cause acute folic acid deficiency, induce a variety of congenital anomalies in humans. It was recently shown that supplementing folic acid to women who previously gave birth to children with neural tube defects significantly reduced the recurrence rate of these defects in subsequent pregnancies and prevented the first occurrence of them.[111,112]* The Centers for Disease Control has recommended that all women in the childbearing age capable of becoming pregnant should consume daily at least 0.4 mg of folic acid, either from diet or from supplements. Zinc deficiency is teratogenic

*See also N. C. Rose, MD, and M. T. Mennuti, MD, "Maternal Serum Screening for Neural Tube Defects and Fetal Chromosome Abnormalities," on pages 312-317.

in animals and has been implicated to be teratogenic in humans as well.[11]

Maternal Diseases

The most important maternal disease causing an increased incidence of fetal congenital anomalies is diabetes mellitus, especially insulin-dependent diabetes mellitus (type I). The incidence of congenital anomalies among the offspring of women with diabetes increases in direct relation to the severity of the disease. In women with type I diabetes and nephropathy, retinopathy, or both, the incidence of malformations may be three to four times higher than in the general population.[113,114] It is important for pregnant women with diabetes to achieve strict control of their blood glucose levels as early as possible, preferably before conception. Because most congenital anomalies occur during the first two months of gestation, the control of the disease after that period will not reduce the incidence of anomalies. Even good control of diabetes during pregnancy may still result in a higher-than-normal incidence of congenital defects in the offspring.[115] Although gestational diabetes is not associated with a higher incidence of congenital anomalies in the offspring, serum from women with gestational diabetes was found to be teratogenic in rat embryos in culture, probably because of the abnormal levels of glucose and ketone bodies.[115]

Teratogen Information Services

Over the past few years, public awareness of the possible teratogenic effects of in utero exposures on the fetus has been growing. This has led to a need for teratogen information services as a part of comprehensive prenatal care programs. Teratogen information services provide information on the effects of chemical, physical, or infectious agents on fetuses to pregnant women and physicians or other professionals in the medical and paramedical services. The information given pertaining to each exposure takes into account the developmental stage of a fetus at exposure, the duration of exposure, the dosage, and the medical history of the mother and family. Most of the services are telephone services, with the caller being interviewed in person in rare instances. In most cases, the risk evaluation can be given directly to the caller during the original phone call. In other cases, a more thorough review of the literature is necessary, and the caller is requested to call back within a few days. Most services also send a written response summarizing the case, the risk evaluation, and any recommendations for prenatal testing or pregnancy interruption. The experience in our center, now starting its seventh year, involves 5,600 calls. We found that in about 75% of calls, the exposures did not increase the risk of malformations to the fetus. In 15%, there was a slight increase in the risk of malformations, estimated to be less than 1%. In 4% to 5%, the precise risk to the fetus could not be estimated. In 5% of the calls, there was a substantial increase in the risk of congenital anomalies, and the callers were informed of this increased risk.[116] The most important task of a teratogen information service is to reassure anxious mothers whenever there is no increased risk to their fetuses.

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Ethical Considerations in Prenatal Diagnosis

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Prenatal diagnostic testing raises a number of important ethical issues, some related to diagnostic testing in general and others related to the special circumstances of pregnancy. These issues are most effectively addressed in the context of a broader understanding of the goals of prenatal diagnosis. Our dual obligations—to the pregnant woman and to the fetus—have an important influence on the goals of testing. Testing seldom leads to treatment beneficial to the fetus, but more often can be beneficial to the pregnant woman, particularly if the information provided enhances her ability to make sound decisions about reproductive matters. The process of prenatal diagnostic testing can, however, limit a woman's sense of control over the decisions made about her pregnancy. It can also provide an opportunity for third parties to become involved in what are usually considered private matters. It is therefore important that the process of testing include adequate counseling and follow-up and that the patient's confidence be respected. As prenatal diagnostic technology expands, both in terms of patients to be tested and diagnoses to be sought, society will face difficult questions concerning access to testing and the justification for its use.

(Gates EA: Ethical considerations in prenatal diagnosis, *In* Fetal Medicine [Special Issue]. West J Med 1993; 159:391-395)

Prenatal testing for the diagnosis of particular fetal conditions has become an important component of prenatal care for many women. Testing methods range from noninvasive technologies such as ultrasonography to invasive intrauterine techniques such as amniocentesis, chorionic villus sampling, and umbilical cord blood sampling. This testing raises a number of important ethical issues, including many common to diagnostic testing in general: the issues of informed consent, the appropriate indications for testing, privacy, confidentiality, and the just allocation of testing services and follow-up treatment.

Because this testing occurs within the context of pregnancy, important additional ethical considerations arise. The increasing availability of diagnostic and therapeutic procedures directed specifically toward improving fetal health has led some observers to consider the fetus to be a patient in its own right, a patient towards whom the obstetrician owes a duty of beneficence, even though the fetus resides within the body of a pregnant woman.[1-3] A good deal of controversy exists over the appropriate application of the concept of the "fetal patient" and includes discussions of the role of the pregnant woman as primary decision maker in matters regarding fetal well-being.[4-6]*

"Autonomy is the moral right to choose and follow one's own plan of life and action."[7(p49)] Although the fetus is deserving of an obligation of beneficence on the part of the obstetrician, it is not an autonomous individual. It cannot be considered a patient in the same sense that the pregnant woman is.

Meaningful consideration of the ethical issues that arise in prenatal diagnostic testing requires a clear sense of the goals of the testing process. In the context of pregnancy, testing may be directed toward the maternal patient, the fetus, or both. The goals of testing will differ depending on which of these parties one posits as the possible beneficiary.

The Fetus

Diagnostic tests are generally used in medicine to benefit the person affected by the disease that a test reveals, while avoiding harm out of proportion to the benefit that the testing can provide. If a physician considering prenatal diagnostic testing regards the fetus as the intended beneficiary, this concept of the goals of testing becomes a problem.

Current methods of obtaining material for prenatal testing often involve risk to the fetus; the possible benefit to the fetus is less clear. The effective treatment of fetal

*See also the article, "Ethical Issues in Recommending and Offering Fetal Therapy," by F. A. Chervenak, MD, and L. B. McCullough, PhD, on pages 396-399.

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conditions is certainly the ultimate aim of much of the technology developed in the area of prenatal diagnostic testing. Currently, however, actual benefit to the fetus or to the expected child can be achieved in only a few situations. When fetal anemia develops due to isoimmunization, prenatal therapy can be effective.[8] Physicians have had some success in treating immunodeficiency syndromes by fetal bone marrow transplantation.[9] The future child may also benefit if the condition diagnosed indicates a change in obstetric management. For example, if hemophilia is diagnosed in a fetus, scalp sampling and the use of a vacuum extractor to assist in delivery can be avoided for the protection of the newborn.

Unfortunately, prenatal testing has not yet led to meaningful therapy for fetuses affected with most of the conditions that can be identified. Even when treatment becomes possible before birth, difficult decisions about the relative risks of treatment, the effectiveness of the therapy, and the need for ongoing and potentially burdensome interventions will remain. One set of conditions for which prenatal diagnosis is frequently used, chromosomal aneuploidy, will probably never be ameliorated through fetal therapy. Selective abortion of the affected fetus will remain an important alternative.

This observation calls into question the appropriateness of much of what is available in terms of diagnostic testing and, particularly, invasive testing, if it is in fact intended to benefit the fetus. Currently used procedures generally involve risk, seldom lead to benefit for the fetus, and often result in a decision for selective abortion. The professional ethics of medicine prohibit the active killing of patients.[10,11] Physicians owe their patients a duty of nonmaleficence—an obligation to avoid doing harm. Whether sparing a fetus a future life of disease, pain, or disability is a benefit or even an avoidance of harm to that future child is a difficult ethical question on which a spectrum of articulate opinion exists.[12-14] If a postnatal life with Turner syndrome or even a more serious condition such as Down syndrome is considered a life worth living, it is difficult to conceive of selective abortion as a benefit or even an avoidance of harm for that potential child.[15]

The power to diagnose fetal conditions exceeds the power to treat them and probably will for a long time to come. Although future investigation may well lead to therapies for many genetic conditions and therefore be of benefit to fetuses and children, the conditions that are now most frequently diagnosed prenatally are ones that will, most likely, never be amenable to meaningful therapy. In these cases it is difficult to conceive of most testing as being beneficial to a fetus in any important way. Whereas the quest for fetal therapy may justify ongoing research in prenatal diagnosis, it does not justify the current expansion in the clinical use of this technology. Another goal for therapy would have to be postulated to support this practice.

The Pregnant Woman

Although the cells being analyzed belong to a fetus or fetal-placental unit, they are obtainable only by traversing the body of a pregnant woman. Whereas the condition being diagnosed is one affecting the fetus, the pregnant woman is the source for any decision that will be made in response to that diagnosis. Despite the fact that the pregnant woman does incur some risk, both physical and psychological, during the process of testing, she may benefit in terms of her ability to make reasoned choices about reproductive matters when test results are received.

Before a test is used in a clinical setting, physicians who intend to use it have an obligation to be certain that the test will provide results that are accurate and reliable. Furthermore, those recommending a diagnostic test must be confident that the test will, in general, yield the benefits that are its goal. If a pregnant woman is intended to be the beneficiary in most instances of prenatal diagnostic testing, and if the benefit expected consists of an enhancement of her ability to exercise informed reproductive choice, then it is important to assess whether that benefit is in fact being achieved. Making choices about pregnancy is a complex and personal process that takes place in the context of ongoing relationships with spouse, family members, and others. It involves the consideration of deeply held personal values and an assessment of one's life circumstances. The process of and response to prenatal diagnostic testing may therefore have an effect on many areas of a woman's life. The sum of these positive and negative effects will determine whether, overall, prenatal diagnostic testing is of benefit to her.

Reassurance

One way in which prenatal testing might benefit a pregnant woman would be by providing reassurance to her about the health of her fetus. Although testing—at least α-fetoprotein and chromosomal testing—tends to raise anxiety before the procedure and while test results are being anticipated, most women experience a decrease in anxiety levels to or below their baseline once normal results are received.[16-20] A group of women who received abnormally low results on α-fetoprotein screening were noted to be substantially more worried about their babies' health three weeks after testing—after normal follow-up results were available—than were women who received an initial normal result. These differences were not appreciable at later points in the pregnancy.[21] Dixson and co-workers observed women who received genetic counseling and then either underwent amniocentesis or declined.[17] The rate of continuing concern about possible congenital abnormalities was just over 20% in both the group who received normal amniocentesis results and in the group of women who declined testing.

The issue of reassurance can also be examined in the converse. Can the information that is obtained through prenatal diagnosis be falsely reassuring? Even if the specific diagnosis being sought, such as muscular dystrophy, is ruled out, approximately a 3% chance remains that the child will be born with some kind of congenital disorder or genetic disease. Will women who undergo prenatal genetic testing be more prepared or less prepared for other congenital problems that may arise?

Enhancing Autonomy

Eric Cassell, a physician and medical ethicist, has stated that "the . . . function of medicine is to preserve . . . autonomy."[22(p18)] This is consistent with the concept that an important goal of prenatal diagnostic testing is to enhance a pregnant woman's ability to make good choices about her pregnancy. Although it is true that prenatal diagnostic testing provides options to women at risk for bearing children with genetic diseases or other congenital conditions, it is not clear from existing data that reproductive choice is actually enhanced. Rapp has asked whether amniocentesis offers women "a 'window of control' or an anxiety-provoking responsibility."[23(p109)] Lippman notes that "some features of prenatal diagnosis do increase control but allocate it to someone other than a pregnant woman herself."[24(p34)]

Several concerns have been articulated regarding the influence of prenatal diagnosis on a woman's sense that the decisions made about her pregnancy are really her own. One survey of women undergoing amniocentesis or chorionic villus sampling indicated that 75% of them found it difficult to refrain from a prenatal diagnostic study once it was offered.[25] Of these women, 78% felt it would be more difficult to give birth to a disabled child if they had not accepted prenatal diagnosis. Many stated that whereas they felt "free from external pressure," they still felt an "obligation" to have testing done.

Among women of a certain age, a willingness to undergo prenatal diagnostic testing seems to be construed as a sign of responsible parenting. Is a woman acting irresponsibly in the eyes of others if the procedures are forgone? Might a woman sense less sympathy and support if testing is forgone and a child is born with a diagnosable condition or if a pregnancy is continued in the face of adverse results? If perceptions such as these are common among pregnant women, the availability of prenatal diagnosis may in fact limit autonomy rather than enhance reproductive choice.

Privacy

The availability of prenatal genetic testing has brought the interests and influence of family, friends, and society into a woman's pregnancy to an increasing degree. It has allowed third-party involvement in the most private of decisions being made during pregnancy. Involvement by parties such as employers and insurance companies in a woman's decisions about prenatal genetic testing could restrict reproductive choice in an unprecedented way.[26]

In one illustrative case, a pregnant woman whose living child was affected with cystic fibrosis sought prenatal testing for the disease. When testing revealed that the expected child would also be affected with cystic fibrosis, the woman and her husband faced an agonizing decision. They ultimately decided not to abort the fetus. Their health maintenance organization, which had originally approved the test, decided that it would not provide medical coverage for an affected child, a child who would be born with a "preexisting condition" because of the prenatal diagnostic procedure. As one journalist wrote, "The insurance company's message was clear: The parents could either abort the defective baby or struggle alone with the financial burden of a sick child" (L. Thompson, "The Price of Knowledge: Genetic Tests That Predict Dire Conditions Become a Two-Edged Sword." *The Washington Post*, October 10, 1989, WH7, col 1). Although the health maintenance organization ultimately capitulated and agreed to cover the child's treatment, its initial policy serves as a sign of the new limits on maternal choice that may evolve as the capacity for prenatal diagnosis expands.

Options

Given the current inability to effectively treat most conditions diagnosed in utero, many women who learn through prenatal testing that their fetus is affected have only two options: continue the pregnancy, anticipating and preparing for the birth of a child with expected handicaps, or terminate the pregnancy. Many women who undergo testing have not yet made a decision as to which option they will choose if testing indicates an abnormality.[17,25] Testing should not be contingent on a woman's willingness to undergo abortion. Although a substantial proportion of people do not consider abortion a morally acceptable alternative, others see it as an important reproductive option, particularly in the context of a prenatal diagnosis.

Although state legislatures in this country are planning and establishing programs to enable women, through genetic screening and prenatal diagnosis, to avoid conceiving or bearing children with serious congenital conditions, a trend toward limiting a woman's right to decide to abort an affected fetus is evident. It seems likely, in view of recent Supreme Court decisions, that state legislatures will have increasing power to define the circumstances under which abortion will be legally available.[27] Although many are currently optimistic that abortion will remain a legal option in this country, women are still faced with limitations on the accessibility of abortion services in terms of the number and geographical distribution of facilities offering abortion procedures. Women facing the termination of a desired pregnancy based on an abnormal outcome from prenatal testing may have even more difficulty because they must locate facilities that offer the termination of second-trimester pregnancies. If access to abortion is substantially restricted, one really must ask just what kind of choices prenatal diagnostic testing offers. How much benefit is knowledge in the absence of meaningful options?

If enhanced decision making on the part of pregnant women is the outcome that justifies using prenatal diagnostic testing, a generally invasive and somewhat risky technology, it is important to demonstrate that the technology actually achieves this end before testing is applied widely, not only to those women at increased risk for having an affected fetus, but to women in general. Investigation of the effect of prenatal testing on pregnant women and their ability to make thoughtful and uncoerced decisions about pregnancy should continue. Efforts to im-

prove the current testing process so that the benefits to pregnant women are increased will also be important.

Counseling

The importance of the nonclinical implications of test results, and the acknowledgement that a woman's personal values are of primary importance in the decision being made, are two of the considerations that underlie the concept of nondirective genetic counseling.[28] To enhance decision making by a patient, pretest counseling should provide accurate information about the testing procedure and the risks involved, including the possibility of ambiguous results. Both the medical and social consequences of the proposed tests and their results should be discussed. Counseling should also include a discussion of the particular condition or conditions for which testing is being done. A patient's informed consent for testing must then be obtained. All of this presumes a certain level of expertise on the part of the person providing the counseling. At present, it is unlikely that most women's health care professionals are as skilled as trained genetic counselors in either genetic knowledge or in the technique of counseling.[29] It may be difficult for many professionals to help patients identify personal preferences while avoiding the implicit communication of their own. There is evidence, for example, of an increased tendency for women to terminate a pregnancy affected by a sex chromosome abnormality when counseled by a general obstetrician rather than a geneticist.[30]

As the use of prenatal diagnostic testing expands, the current shortage of genetic counselors will be exacerbated.[31] Most women, particularly those who are offered testing as a routine part of prenatal care, will be counseled by their regular obstetric professional. These professionals are obligated to improve their skills so that their patients may benefit from the process of testing and so that the burdens that are a part of testing do not, on balance, result in harm.

Throughout the process of testing, it is essential that women feel assured that information shared with their health care professional will be held in confidence. Information obtained through prenatal testing should not be revealed to institutional third parties such as insurance carriers or employers without a woman's explicit consent.[32] The permissibility of sharing information about genetic diagnoses with other family members who are at risk, without the consent of the person being tested, is currently a matter for debate.[33,34] As a rule, patient confidentiality should be respected. A breach of confidentiality may be justified if the conditions set forward by the President's Commission for the Study of Ethical Problems in Medicine are met[35(p44)]:

- Reasonable efforts to elicit voluntary consent to disclosure have failed;
- A high probability exists that harm will occur if the information is withheld and the disclosed information will actually be used to avert harm;
- The harm that identifiable persons would suffer would be serious; and
- Appropriate precautions are taken to ensure that only the genetic information needed for diagnosis or treatment, or both, of the disease in question is disclosed.

Applying an Expanding Technology

In most circumstances, the process of prenatal diagnostic testing more effectively benefits a pregnant woman than it does the fetus actually being tested. Nevertheless, the obstetric professional still maintains important obligations to both parties. What effect does this dual obligation have when decisions are made about which conditions are reasonable targets for prenatal diagnosis?

Juengst has proposed that the range of appropriately diagnosed conditions be limited to those "relevant to the welfare of the fetus."[36] This approach, by providing information relative to the health of the fetus, can help parents make decisions in the context of fetal health. It also confines the process of prenatal diagnostic testing to the "usual context of medical practice," that is, health. Even within these limitations, however, decisions will be required as to the appropriateness of prenatal diagnosis and selective abortion for mild impairments such as von Willebrand's disease, treatable conditions such as phenylketonuria, late-onset conditions such as Huntington's disease and Alzheimer's disease, or the increased susceptibility to a condition such as coronary artery disease. As Botkin points out, "This technology will force us to examine the fundamental relationship between parent and child. How much control can we legitimately exert over the biologic structure of our children and how would such control change the way we view our children, how they view us, and how they view themselves?"[37(p104)] If a societal consensus on questions such as these cannot be reached, individual choice is likely to remain decisive.

Economic considerations may constrain our ability to provide prenatal diagnosis for conditions such as those just listed. Legitimate concern already exists about inequalities in access to what are currently considered routine prenatal diagnostic services. Many of these inequities reflect society's problems with access to prenatal care in general. If the affluent continue to have disproportionate access to technologies such as chorionic villus sampling and amniocentesis, being genetically disabled could become, as much as anything, a mark of social class.[34] This sort of inequity may increase as noninvasive screening technologies, such as the use of the "triple marker,"* become widely available.[38] A larger segment of society will have access to testing, with the exception of those with limited access to health care in general. As we face decisions about the wisest use of health care resources, a technology that provides options or enhances choice may not appear as essential to the public health as a technology that provides cures.

Conclusion

As perinatal medicine advances, more interventions will become possible, enhancing the potential benefit of

*See N. C. Rose, MD, and M. T. Mennuti, MD, "Maternal Serum Screening for Neural Tube Defects and Fetal Chromosome Abnormalities," on pages 312-317.

testing and expanding the treatment options available for affected fetuses. A substantial proportion of testing, however, will continue to be done for conditions such as Down syndrome for which meaningful prenatal treatment, and therefore fetal benefit, is not expected. In these contexts, the pregnant woman, often in conjunction with her partner, will remain the principal beneficiary of the process of prenatal diagnosis. As individual decisions are made about the use of prenatal diagnostic technology, it will be important that obstetric professionals be able to identify the goals of the particular test being considered, in relation to both a pregnant woman and her fetus. Health care professionals will have an important role in helping pregnant women and their partners elicit their own preferences about testing and come to well-considered decisions in response to testing results.

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Ethical Issues in Recommending and Offering Fetal Therapy

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Fetal therapy should be offered and recommended for a viable fetus when these criteria are met: invasive therapy is reliably judged to have a high probability of being life-saving or of preventing serious and irreversible disease, injury, or disability for the fetus and for the child it can become; such therapy is reliably judged to involve low mortality risk and low or manageable risk of serious disease, injury, or disability to the viable fetus and the child it can become; and the mortality risk and the risk of disease, injury, or disability to the pregnant woman is reliably judged to be low or manageable. When one or more of these criteria are not satisfied, intervention is experimental and can only be offered, not recommended, on the basis of benefit to future patients and the autonomy of the pregnant woman.

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With fetal therapy we are able to do routinely for a fetus what other medical fields do—undertake a wide array of diagnostic and therapeutic interventions and conduct research on new interventions. As a consequence, a fetus seems just as much a patient as any other, save for its locale in utero.[1-5] References to the fetus as a patient have become commonplace in the literature and practice of maternal-fetal medicine.[6-13]

The concept of the fetus as a patient has developed primarily as a result of technologic advances and not careful ethical investigation. We carefully examine the concept of the fetus as patient and identify the clinical implications for recommending and offering fetal therapy.

Language of Medical Ethics

To talk of the fetus as a patient is to use the language and concepts of medical ethics, because concern for protecting and promoting the interests of the patient has constituted the foundation for medical ethics since the days of the Hippocratic Oath. In the original version of the oath, a physician swore to do what would benefit the sick while preventing harm to them.[14] In more precise ethical terms, the oath should be understood as asserting ethical obligations based on their benefit to patients. Beneficence requires a physician to act in such a way as to produce a greater balance of good over harm, as understood from a clinical perspective.[15,16] Good and harm have been defined over time on the basis of what medicine as a profession can reasonably claim as its competencies. The good that medicine is competent to achieve is preventing premature death and preventing, curing, or at least managing disease, injury, disability, and unnecessary pain and suffering.[16]

Clinical judgment and ethical obligations based on benefit to patients constituted the whole of medical ethics until the 20th century. Under the influences of United States common law and philosophical ethics, medical ethics in the United States has increasingly come to include acknowledging and emphasizing the importance of patients' perspectives on their interests and what should count as protecting and promoting their interests.[17] A pregnant woman should be presumed to be able to form judgments about her interests on the basis of her own values and express those preferences. Respect for a patient's autonomy requires a physician to acknowledge the integrity of a patient's values in her life, to elicit her preferences, and to assist her in putting them into effect.[18]

The Fetus as Patient—An Ethical Concept

A prominent approach in the bioethics literature to understanding the concept of the fetus as patient has been to try to establish whether or not a fetus has independent

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moral status.[19-31] Independent moral status for a fetus means that one or more characteristics that a fetus possesses in and of itself and, therefore, independent of the mother or any other factor generate obligations to the fetus on the part of the pregnant woman and her physician.

When does a fetus acquire independent moral status? One view is that a fetus possesses independent moral status from the moment of conception or implantation.[32-34] Another is that the fetus acquires it in degrees, thus resulting in graded moral status.[26,28] Still another view, at least implicitly, is that a fetus never has independent moral status so long as it is in utero.[27]

Despite an enormous philosophical and theologic literature on this subject, no agreement on a single authoritative account of the independent moral status of a fetus has been reached.[35,36] This is not surprising because no single methodology would be considered authoritative for all of the diverse theologic and philosophical schools of thought involved in this centuries-old debate. Without such a methodology, agreement is impossible. For agreement ever to be possible, deep divisions about such a final authority within and between theologic and philosophical traditions would have to be resolved in a way satisfactory to all, and this is inconceivable. It is best to turn to an alternative approach that makes it possible to identify ethically distinct senses of the fetus as patient and their clinical implications.

We start with the claim that being a patient does not require that one possess independent moral status.[25] Instead, being a patient means that one can benefit from the application of the clinical skills of a physician. A human without independent moral status is properly regarded as a patient when that human is presented to a physician for the purpose of applying clinical interventions that are reliably expected to result in a greater balance of good over harm in the future of the person in question. In other words, someone is a patient when a physician has benefit-based ethical obligations to that person.[18,37,38]

A fetus is a patient when medical interventions can be reasonably expected to result in a greater balance of good over harm for the child the fetus can become. The ethical importance of the concept of the fetus as patient, therefore, depends on links that can be established between a fetus and the child it can become and not on the alleged—and always disputable—independent moral status of the fetus. One such link is viability.

The Viable Fetus as Patient

Viability establishes a basis for the first ethical sense of a fetus as patient. Both biologic and technologic factors are required for a viable fetus to exist ex utero and thus become a child.[36,39,40] These two factors do not exist as a function of the autonomy of the pregnant woman. When a fetus is viable—when it is of sufficient maturity that it can survive into the neonatal period and become a child with independent moral status, even if it requires technologic support—the fetus is a patient.[38] Benefit to the viable fetus must, of course, be considered, together with the benefits and the autonomy of the pregnant woman.[18,38]

The Previable Fetus as Patient

The only possible link between the previable fetus and the child it can become is the pregnant woman's autonomy. This provides the sole basis for the second ethical sense of the fetus as patient. Technologic factors cannot result in the previable fetus becoming a child, because this is what previable means. A link, therefore, between a previable fetus and the future child can be established only by the pregnant woman's decision to confer the status of patient on her fetus. The previable fetus, because it cannot reliably be thought to possess independent moral status, has no claim to the status of patient independent of the pregnant woman's autonomy.

It is important to appreciate that this second sense of the fetus as a patient includes in vitro embryos. Simply being presented to a physician does not make the in vitro embryo a patient. Whether the fetus is a patient depends as well on links that can be established between the fetus and its future—the child with independent moral status. Therefore, the reasonableness of medical interventions on the in vitro embryo turns on whether that embryo later becomes viable. Otherwise, no benefit of such intervention can be meaningfully said to result. An in vitro embryo, therefore, becomes viable only when it survives in vitro cell division, transfer, implantation, and subsequent gestation to such a time as it becomes viable.

Whether an in vitro embryo will become a viable fetus and whether medical intervention on such an embryo will benefit the fetus are both functions of a pregnant woman's autonomy. The in vitro embryo is a previable fetus and becomes a patient only when the woman into whose reproductive tract the embryo(s) will be transferred confers that status.[37,38] Whether the in vitro embryo is a patient is therefore not a function of the sperm donor's autonomy. A woman is free to confer with the sperm donor as she chooses.

Fetal Therapy and the Ethical Standard of Care

Whether fetal therapy can be judged to be the standard of care on ethical grounds depends on the clinical implications of the concept of the fetus as patient. Such fetal therapy must reliably be thought, on the basis of documented clinical experience, to benefit the future child. Recall that the ethical content of this concept is to be understood not simply in terms of physical accessibility, but also in terms of whether clinical interventions on the fetus are reliably thought to be efficacious, in that they are reliably expected to result in a greater balance of good over harm for the future child.

Satisfying this condition establishes the standard of care in its initial, benefit-based sense. This ethical concept of standard of care, however, cannot be completely understood until a woman's autonomy is considered.

A pregnant woman is under no ethical obligation to confer the status of patient on her previable fetus simply because there exists a therapy that might benefit the fetus. Whether such therapy is, on ethical grounds, to be judged

the standard of care for her fetus is entirely a function of the pregnant woman's autonomy. Satisfying both conditions is necessary for fetal therapy to be reliably judged to be the ethical standard of care for previable fetuses on ethical grounds.

The same is true for fetal therapy on a viable fetus. Such a fetus is properly judged to be a patient. As we have noted, however, obligations to the fetus must be negotiated with obligations to the pregnant woman. Fetal therapy necessarily involves risks to the pregnant woman; she is ethically obligated to accept reasonable risks to herself only to attempt to benefit her fetus.[18]

The preceding helps to distinguish an ethical from a legal standard of care for fetal therapy. An ethical standard must take account not only of the benefit to the fetus but also of both the benefit to and the autonomy of the pregnant woman. A legal standard of care tends to focus on efficacy and safety, which are based on considerations of benefit applied to both the fetus and perhaps the pregnant woman. The legal standard of care tends to ignore the autonomy of the pregnant woman. This is the fundamental difference between a legal and an ethical standard of care for fetal therapy.

Recommending and Offering Therapy for the Viable Fetus

Fetal therapy should be recommended when the intervention will benefit a fetus and the risks of the intervention are those a pregnant woman ought to accept. We caution that there is no simple algorithm by which a pregnant woman—or her physician—can conclude that she is obligated to accept risk to herself on behalf of her viable fetus. Such an ethical obligation—which should not be automatically equated with a legal obligation—exists when three criteria are satisfied:

- Invasive therapy for the viable fetus is reliably judged to have a high probability of being life-saving or of preventing serious and irreversible disease, injury, or disability for a fetus and the child the fetus can become;
- Such therapy is reliably judged to involve low mortality risk and low or manageable risk of serious disease, injury, or disability to the viable fetus and the child it can become; and
- The mortality risk to the pregnant woman is reliably judged to be low, and the risk of disease, injury, or disability to the pregnant woman is reliably judged to be low or manageable.[41]

When the first two criteria are satisfied, a clear and substantial net benefit to the viable fetus and the child it can become is expected. When the third criterion is satisfied, no clear and substantial net harm to the pregnant woman is expected. Given the expected net benefit to the viable fetus and the low risk of harm to the pregnant woman, the latter are risks she should reasonably be expected to accept,[18] for example, as in intravascular transfusion for severe isoimmunization. This moral fact shapes how she should exercise her autonomy in response to her ethical obligations to her fetus.[18,38]

Recommending treatment of the viable fetus is ethically justified, therefore, when these three criteria are satisfied. The burden of ethical proof rests with those who would propose recommending intervention when one or more of these three criteria cannot be satisfied. This should be a matter of further careful investigation and debate in the ethics of fetal therapy.

Forms of fetal therapy that do not meet these criteria should be regarded as experimental. For example, because open abdominal fetal surgery involves risks that no pregnant woman is obligated to accept in order to benefit her viable fetus, all such surgical procedures must, on ethical grounds, be regarded as experimental. No ethical justification exists for recommending experimental fetal therapy because none of the three conditions is satisfied.

How should a physician respond if a pregnant woman with a viable fetus rejects a recommendation of fetal therapy that satisfies an ethically justified standard of care? Informed consent should be the first response. In undertaking a further response, negotiation, the physician should acknowledge and take into account the pregnant woman's assessment of the risks and benefits of invasive fetal therapy to herself and her fetus. One is justified in going beyond negotiation to respectful persuasion, and perhaps even to an ethics committee, as part of a preventive ethics clinical strategy.[42]

Experimental therapy for the viable fetus can justifiably be offered to a pregnant woman. The ethical justification for doing so rests on the three criteria for ethical standard of care defined earlier. By definition, if the first two criteria are not satisfied, no net fetal benefit exists, and therefore there is no obligation to the fetus to offer experimental therapy. If the third criterion is not met (even if the first two are), there is only net harm to the pregnant patient and no benefit to her to offer experimental fetal therapy.

The principal justifications for offering fetal therapy that does not meet the three criteria are to benefit future patients and to enhance the pregnant woman's autonomy by expanding the range of her options. The first justification appeals to an obligation to provide quality medical care to future generations. Both must be made clear to the pregnant woman as part of the informed consent process, so she does not subscribe to the mistaken belief that experimental fetal interventions will benefit her fetus or herself. When referrals are requested for well-developed clinical trials, a physician is obligated to offer the opportunity for enrollment as a research subject—again, only on the justification that research benefits future patients and that it is the woman's decision.

In cases in which the first two criteria are satisfied but the third is not, intervention should be regarded as experimental and only offered, not recommended, to a pregnant woman. Respect for her autonomy requires that she be accorded the opportunity to decide for herself whether she is obligated to risk serious harm for the possible benefit of the fetus and the child it can become. Medicine has no competence to make this judgment.

Recommending and Offering Therapy for the Previable Fetus

When a pregnant woman has conferred the status of patient on her previable fetus and ethical criteria are also satisfied, fetal therapy can ethically be recommended. This is directly analogous to informed consent to therapy for the viable fetus and the strategies discussed earlier apply.

When the pregnant woman withholds or withdraws the status of being a patient from her previable fetus, the situation is directly analogous to experimental fetal therapy. Neither the pregnant woman nor the physician is ethically obligated to regard the previable fetus as a patient. Any discussion of experimental fetal intervention must be strictly nondirective, which is consistent with offering but not with recommending enrollment as a research subject in a clinical investigation trial.[43]

Conclusion

We are aware that some clinicians may feel that an ethical standard of care for fetal therapy that is based in large part on respect for a pregnant woman's autonomy is unrealistic because of the strong, perhaps even coercive, psychological pressure pregnant women may experience when confronted with an imperiled pregnancy and the availability of experimental fetal intervention. We have sought to address the main ethical implication—the possible impairment of the exercise of a pregnant woman's autonomy. The distinction between offering versus recommending intervention is meant precisely as the most powerful antidote to such impairment. There is no reason whatever to believe, and substantial ethical stakes in not acting on the belief, that such self-imposed, psychological pressure is in all cases irreversible and therefore irresistible. Physicians should beware the unjustified paternalism implicit in such a belief.

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Ethics of Fetal Tissue Transplantation

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Now that the Clinton Administration has overturned the ban on federal funding for fetal tissue transplantation, old ethical issues renew their relevance and new ethical issues arise. Is fetal tissue transplantation necessary and beneficial? Are fetal rights violated by the use of fetal tissue in research? Is there a moral danger that the potential of fetal tissue donation will encourage elective abortions? Should pregnant women be allowed to designate specific fetal transplant recipients? What criteria should be used to select fetal tissue transplants? Whose consent should be required for the use of fetal tissue for transplantation? We review the current state of clinical research with fetal tissue transplantation, the legal history of fetal tissue research, the major arguments against the use of fetal tissue for transplantation, and the new post-moratorium ethical dilemmas. We include recommendations for guidelines to govern the medical treatment of fetal tissue in transplantation.

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Human fetal tissue transplantation is still experimental, and trials with animals and humans have shown limited success. But researchers and clinicians agree that, given social and legal support, fetal tissue transplants could soon promise unique therapy for dozens of crippling diseases with substantial morbidity and mortality. Clinical trials with human fetal tissue have already been conducted on patients with Parkinson's disease, insulin-dependent diabetes mellitus, the DiGeorge syndrome, severe combined immunodeficiency, aplastic anemia, acute myelogenous leukemia, thalassemia, Fabry's disease, the Hurler syndrome, and Gaucher's disease. Others have proposed that fetal tissue be used to treat Alzheimer's disease, congenital heart failure, congenital liver failure, congenital kidney failure, and a host of hematologic and endocrine abnormalities in adults and children. The patient population that could benefit from fetal tissue transplants is substantial.

Since *Roe versus Wade* legalized abortion in 1973, pregnant women and their developing fetuses have been at the center of one of the most heated public debates in American history. Scientific journals have steered clear of such politically charged controversy, and several federal panels have found vague language to evade moral stances on abortion. But the promise of fetal tissue therapy in a shifting political climate makes clear the need for opinions to be voiced frankly by the medical community.

We strongly favor the use of human fetal tissue for the purposes of medical therapy, and herein we discuss the current state of clinical research with fetal tissue transplantation, the legal history of fetal tissue research in the United States, the major arguments against fetal tissue transplantation, and a framework for solving ethical problems involving aborted fetuses. We conclude by proposing a set of ethical guidelines to govern medical uses of human fetal tissue.

Using Fetal Tissue for Transplantation

Fetal tissue transplantation may be able to overcome the failures of traditional medical and surgical therapy to ameliorate several diseases, most notably Parkinson's disease and insulin-dependent diabetes mellitus. Furthermore, the use of fetal tissue may be required to develop novel therapies for hematolymphoid diseases.

Medical and Surgical Alternatives

Medical alternatives to fetal tissue transplantation are currently being refined, but long-term cures remain elusive. Most persons with insulin-dependent diabetes currently use genetically engineered human insulin, combined with careful dietary management, to control blood glucose levels. Even with good glucose control, however, the disease progresses, and patients have a relatively early onset of peripheral neuropathy, nephropathy, retinopathy, and heart disease. Patients with Parkinson's disease derive some benefit from the drug levodopa, a congener of dopamine, but even with medication, they continue to ex-

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ABBREVIATIONS USED IN TEXT

NIH = National Institutes of Health
UAGA = Uniform Anatomical Gift Act

perience "on-off" episodes of neuromuscular control, and many young persons lose their ability to function at work and at home. Although multidrug trials with chemotherapy and radiotherapy hold promise for some hematolymphoid diseases, most of these diseases eventually resist medical treatment.

Surgical alternatives are overshadowed by unsatisfactory results and long-term requirements for immunosuppression. Some patients with Parkinson's disease have received autografts and allografts of adrenal medullary cells and xenografts of modified adrenal medullary cells from rodents and primates.[1] Many surgical protocols, however, particularly in the field of adrenal allografts, have been suspended in response to unpromising results.[2] Hematopoietic stem cell replacement is a possible therapy for some immunodeficiencies and hematologic cancers, but the research—much of which uses fetal tissue—is in its infancy.[3]

Although initially hopeful, pancreatic allograft and xenograft results provide little comfort for persons newly diagnosed with diabetes. And although the possibility of isolated islet cell xenografts is being actively pursued, no permanent success has yet been reported.[4] More than 3,000 persons with diabetes have received pancreas transplants during the past 26 years, and the most recent transplants have produced insulin-independent life-styles for 72% of the recipients. Unfortunately, all recipients require immunosuppressive medication, and the one-year mortality rate is about 8%.[5] Thus far, only persons with diabetes who have received kidney transplants and those who are severely impaired are considered for pancreas transplants. As a result, the long-term ability of these allografts to prevent the onset of the diabetic morbidity is untested.

Principles of Fetal Tissue Transplantation

Human fetal tissue is an attractive source of therapeutic transplants because it has two physiologic properties that make it more useful than adult or animal tissue. First, most fetal cells are hyperproliferative and multipotent, meaning that these donor cells are capable of quickly reversing the lost function of a host organ. Second, fetal cells may pose a low immunogenic threat to the cellular defenses of the host.[6,7] Current experiments with adult donor tissue are often limited by deficiencies in these properties.

Research on fetal tissue to develop medical therapy is not new. Fetal tissue research was responsible in the 1950s and 1960s for vaccines against polio and rubella, the treatment of Rh incompatibility, and the prenatal diagnosis of genetic diseases. But the use of fetal tissue as a means of medical therapy is new. Clinical trials with fetal neural, thymic, pancreatic, and hematopoietic tissue are underway internationally.

Fetal Tissue Transplantation in Humans

The only recorded successes with fetal tissue transplantation in humans are in treating Parkinson's disease[7-11] and a rare congenital disorder, DiGeorge syndrome.[12] The most accepted theory to explain Parkinson's disease attributes its cause to a relative deficiency of dopamine produced in the nigrostriatal region of a patient's brain. Operating on this theory since 1987, surgeons have transplanted dopamine-producing neural tissue from first-trimester abortuses into the brains of patients with Parkinson's disease. Results with 13 patients in three separate studies vary according to surgical technique and patient selection, but fetal tissue transplantation does improve self-assessed quality of life; it decreases the frequency and intensity of "freezing spells"—a characteristically disabling feature of the disease—and decreases the required dosage of levodopa.[8-10]

For more than 20 years patients with DiGeorge syndrome, an immunodeficiency resulting from the absence of thymus and parathyroid tissue at birth, have been known to respond well to transplants of fetal thymus tissue.[12]

Preliminary results with fetal tissue transplantation for other human diseases show little success. Fetal pancreatic tissue has been shown to reduce exogenous insulin requirements in humans with insulin-dependent diabetes, but only transiently.[13] Because fetal liver tissue is a robust source of pluripotent hematolymphoid cells, it has been used experimentally to treat hemophilia, severe combined immunodeficiency, aplastic anemia, and acute myelogenous leukemia. These treatments have produced minimal success, but most have been done late in the natural progression of the disease, after standard chemotherapeutic trials have failed.[10] In utero transplants to treat hematologic and immune deficiencies are being widely investigated in animals[14,15] and in humans.[16-18] Several medical and scientific organizations have concluded that fetal tissue transplantation will be a vital part of cellular therapy in years to come.[10]

Need for Tissue From Elective Abortions

During a 1991 Senate debate, the Bush Administration proposed an amendment that established a national network of tissue banks authorized to store only tissue from spontaneously aborted fetuses and ectopic pregnancies.[15] The tissue bank, administered through five national centers, cost $6 million to establish.[19] For logistical reasons, however, future success in human fetal tissue transplantation cannot depend on tissue from spontaneous abortions, stillbirths, and ectopic pregnancies. Unlike that from elective abortions, tissue from at least 60% of spontaneous abortions contains severe genetic defects. Even without genetic defects, a large percentage of these fetuses do not have enough differentiated tissue to be therapeutically useful. Of spontaneous abortions, only 3.8% (or about 28,000 fetuses) each year would provide tissue theoretically eligible for transplantation, but this figure includes many fetuses that are practically ineligible for transplantation because they died much earlier in utero or

because they were never karyotyped to rule out trisomy. Of ectopic pregnancies, 21% to 49% (18,000 to 43,000) are morphologically intact, but only 1% (880) are unassociated with tubal hemorrhage, a common cause of early organ death in fetuses.[20] The combined conservative total represents less than a third of the annual population diagnosed in the United States with Parkinson's disease and insulin-dependent diabetes mellitus. This low yield, combined with the burden of obtaining specimens from unscheduled events that often occur at home or in an emergency department, makes transplantable tissue from spontaneous abortions and ectopic pregnancies effectively inaccessible.

Legal History of Fetal Tissue Research

Although fetal tissue transplantation has been experimental in the United States since the 1930s, legal controversy over fetal tissue research did not arise until immediately after the Supreme Court's *Roe versus Wade* decision. On April 12, 1973, a 200-person protest organized by a Catholic girls' school persuaded a National Institutes of Health (NIH) official to voice publicly the government's opposition to the use of "live" fetal tissue for research. The next day, New York Representative Angelo Roncallo introduced legislation to ban all fetal tissue research in the United States.[21]

Political action on fetal tissue research remained dormant until March 1988, when Robert Windom, President Reagan's Assistant Secretary of Health and Human Services under Otis Bowen, imposed a moratorium on fetal tissue research for transplantation purposes, pending the recommendations of a 21-member NIH panel. After two days of public hearings and three months of deliberation, the panel concluded that funding human fetal tissue transplantation was acceptable public policy. Despite such institutional support for fetal tissue research, Secretary of Health and Human Services Louis Sullivan extended indefinitely the moratorium on federal funding of fetal tissue research for transplantation.

Separate measures to overturn the funding moratorium, appended to an NIH appropriations bill, passed in the House of Representatives in 1991 and in the Senate in 1992. Senate support was heavily influenced by personal appeals, including Republican Strom Thurmond's plea on behalf of his daughter, who has diabetes.[22] New legislation would have funded research on tissue donated from elective abortions, subject to clear evidence that "the decision to make the donation is made separately and independently of the decision to undergo the abortion."[23] But Senate filibustering at the end of the last congressional session in 1992 allowed the bill's demise.

Soon after taking office in 1993, President Clinton overturned by executive order the moratorium on federally funded fetal tissue transplantation. Since then, there has been a notable increase in grant applications to the NIH for proposals to use fetal tissue in experimental transplantation, and Congress is authorizing the Department of Health and Human Services to oversee the conduct of this research.

The Fetal Tissue Transplantation Debate

During the 1988 NIH panel hearings and during congressional debate concerning fetal tissue research, a common list of ethical questions was addressed:

- Is fetal tissue transplantation ethically acceptable? Should the integrity of a human fetus place it in a class entirely separate from that reserved for other biologic gifts, such as blood, kidneys, and hearts?
- Should fetal tissue acquired from elective abortions be exempted from research uses? Should a woman not be allowed to play contradictory roles as agency in a fetus's death and as proxy to authorize donation of the fetus's tissue?
- Must a pregnant woman give consent to allow her fetus's tissue to be used for research purposes?
- Should a woman be permitted to abort a fetus to provide transplantable tissue for a relative?
- Will fetal tissue transplantation indirectly encourage women to choose abortions? If so, is this effect ethically permissible?

It is not the task of ethical analysis to answer these questions definitively. Various polling organizations have already gauged popular opinion, and the results are not surprising. A survey of college students indicates support for federal funding of fetal tissue research and opposition to the idea of women designating specific fetal tissue transplant recipients.[24] Nor have centuries of ethical analysis created political consensus. Legislators, governors, judges, and the electorate may long continue to debate the wisdom of *Roe versus Wade*, the public funding of family counseling, and the public's access to experimental procedures. In 1989, the Stanford University Medical Center Committee on Ethics, composed of 48 representatives of the university community, agreed that human fetal tissue research, when subject to the legal rules of the Uniform Anatomical Gift Act (UAGA) and a prohibition against a woman's designating specific recipients of fetal tissue, is ethically acceptable.[25]

Our ethical analysis will suggest a responsible direction for public debate about fetal tissue transplantation, which operates under the assumption that in the prevailing legal climate of the United States, abortion performed under informed consent is ethically acceptable.

Is a Fetus a Person?

Whereas abortion may be ethically acceptable, the actual practice remains inherently distasteful to most persons. In fact, without such a prevalent distaste for abortion, this entire discussion would be moot. Abortions would be neutral events, and fetuses would be neutral products of those events, openly accessible to researchers and clinicians.

The equivocacy of personhood is a central reason for this distaste. When during gestation does a fetus become a person, with accompanying rights? How do we identify a fetus as dead or alive, viable or nonviable? Do the answers to these questions have any bearing on the

postabortion use of fetal tissue? These questions are best approached at three points during fetal existence:

• Personhood after fetal death is accepted by most ethicists and legal scholars as the easiest to assess.[26] Regardless of its antemortem status, a dead fetus claims the same rights as a dead person. As with any human cadaver, the closest relative or guardian of the deceased has whole authority over the disposition of the fetal cadaver.

• Personhood in utero, before viability, is difficult to assess ethically, largely because fetal viability is difficult to define medically. Medical judgment generally labels previable any fetus less than 24 weeks' gestational age (about 500 grams), estimated by ultrasonic measurement of the fetal anatomy. At this stage, it is generally agreed that, even with extraordinary medical treatment, fetal lungs are incapable of operating independently. Most states permit elective abortions to be done on fetuses under 20 weeks' gestational age. This definition was established, however, before the successes with intra-alveolar surfactant treatment and extracorporeal mechanical oxygenation, which now enhance the long-term survival of infants weighing less than 750 grams (26 weeks' gestation).

• Fetuses ex utero and alive create the greatest challenge to an ethical critique of fetal tissue transplantation. Abortion procedures depend on the gestational age at which they are done. During the first trimester (before 12 weeks), a fetus is removed by suction and curettage techniques. During the second trimester, a fetus can be delivered live after the induction of labor, or more commonly, the fetus can be dismembered in utero and the fetal parts manually extracted. The second-trimester procedures sometimes, although rarely, produce fetuses whose cardiovascular and brain-stem functions remain operative for several hours ex utero.[27] More than 90% of abortions performed in the United States are done during the first trimester,[28] and most current research with transplantation for Parkinson's disease and diabetes mellitus uses tissue from fetuses aborted during the first trimester.

Ethical problems exist only for those rare second-trimester abortions that produce whole, live fetuses. It must be assumed that during this time period, when the fetus ex utero is alive, it claims the concomitant rights of personhood. Strong ethical and legal principles argue against the use of tissue from fetuses during this period. Under the principles of the Nuremberg Code and the Helsinki Declaration, nontherapeutic experimentation without a subject's informed consent is unethical, particularly if that experimentation is harmful to the individual.[29] United States judicial precedent argues against the authority of parents or guardians to consent by proxy to the nontherapeutic use of a child's organs to save the life of another child.[26] (The state assumes the role of *parens patriae* to resolve a conflict of interest between the emotional needs of the guardians and the life-claiming needs of the child.) Although not absolute, the same legal principle can be used to argue against the donation of a kidney from a dying anencephalic infant.

It follows logically, therefore, that the transplantation of tissue from live fetuses ex utero should be prohibited. Tissue from second-trimester abortions should, however, be available for transplantation immediately after fetal death has been declared by a qualified physician. A woman should be allowed to consent to the use of tissue from a dead fetus during the antemortem period, and there is no ethical proscription against subsequently informing a researcher of the impending death.

Bad Science

Beyond the debate about fetal personhood, the following arguments against the use of fetal tissue for transplantation to living humans are commonly presented:

• The results of animal and human research trials have not been encouraging, medical alternatives to fetal tissue transplantation exist, and the potential benefits of such transplantation do not reduce mortality. A careful review of the literature by a British ethicist concludes that "the case for utilization of human foetal pancreas in transplantation is in no way strengthened by the results of animal experimentation."[27(p58)] Medical therapy for parkinsonism, diabetes, and hematologic disorders is available, and unlike heart-lung and kidney transplants from adult cadavers, fetal tissue transplants do not represent immediate, life-saving treatment.

Although the claims of possible benefits from fetal tissue transplantation are admittedly guarded, we should not prohibit continued research and clinical trials in this field. The Helsinki Declaration, which demands that successful trials in animals precede human trials of experimentation, allows clinicians and researchers to judge the meaning of the word "success." The most important element of an experimental trial is an effective process for affording the transplant recipient full and informed consent. Perhaps scientific critics of fetal tissue transplantation should be welcomed to review this informed consent process, but they should not ask for artificial means (such as a blanket moratorium) to slow the pace of clinical research.

• The scientific use of fetal tissue welcomes abortion as "good," a necessary precursor to advances in medical therapy. By extension, opponents claim, society would be supporting the institution of abortion. This runs directly against a prevailing American sentiment that prefers to condone abortion, not to afford it any independent admiration.

"Science, since people must do it, is a socially imbedded activity," writes Stephen Jay Gould in *The Mismeasure of Man*, a historical treatise that argues for social accountability in science.[30(p21)] Scientists and clinicians make implicit social judgments with every primate experiment, every drug toxicity screen, and every private research institution newly incorporated. There is no ethical proscription against American scientists implicitly supporting women's access to abortion procedures. Those researchers and physicians who object to abortion are under no obligations to participate in procedures associated with fetal tissue transplantation.

Encouraging Elective Abortions

According to the most-often-voiced argument against fetal tissue transplantation, the life-enhancing potential of the procedure may encourage more abortions. Opponents argue that by adding something "good" to a distasteful procedure, fetal tissue transplantation may encourage more women to opt for abortions. Worse yet, the marketability of fetal tissue may encourage indirect ways of increasing the abortion rate. Hypothetical slippery slopes run rich in this argument. Imagine the following plausible scenario:

In mid-1993, a phenomenally successful procedure to treat male-factor infertility requires the transplantation of testicular cells from fetal tissue of more than 14 weeks' gestation. (Elective abortion and infertility therapy share common properties: neither are funded by public insurance, and neither are recognized as life-threatening.) Less than half of all aborted fetuses are eligible to provide such tissue, and because of the approval by the Food and Drug Administration for mifepristone (RU 486), the incidence of elective abortions nationwide is declining. A shortage of tissue develops. Meanwhile, private medical corporations market the treatment to thousands of infertile men, creating an increased demand. Because of these pressures, the incidence of abortion increases.

The claims are threefold: that the abortion rate will increase, that an increasing abortion rate is wrong, and that the influences that will create this increasing abortion rate are wrong. The first claim is wildly speculative, but for the purposes of this ethical analysis, it may be conceded. The second claim has already been discussed: namely, that although abortion may be distasteful, its exercise in the United States is ethically acceptable. The third claim requires further consideration.

Fetal Tissue Donation and Decision-making Autonomy

To understand why the third claim of the argument is untenable, we must first define "influence." Faden and Beauchamp depict a graded continuum of influences on a patient's decision-making process.[31] The goal of their analysis is to identify what they call "substantially controlling influences" that unduly compromise autonomous decision making. At one end of this continuum is rational persuasion, the art of convincing the family of a febrile patient with mental status changes, for example, to provide consent for a lumbar puncture. Persuasion falls entirely within ethical boundaries because it is a noncontrolling influence. At the other end of the continuum is coercion, strictly defined as any irresistible threat that causes a person to do something they otherwise would not do. Coercion exists when a researcher threatens to fire an employee unless that employee participates as a research subject. Coercion is ethically impermissible.

The middle ground on the continuum is manipulation, which may or may not be "unduly controlling." The US Public Health Service was unethical when it unduly manipulated (some claim "exploited") economically deprived men to participate in the Tuskegee (Alabama) syphilis experiments by providing irresistible offers of free food, medication, and burial assistance.[32] A professor would be within ethical boundaries, however, in offering extracredit points to students who enroll as research subjects because the offer is both welcome and (under the provision perhaps that a "B" not be convertible to an "A") resistible.[34]

Certainly any financial reimbursement for fetal tissue donation is ethically unconscionable because it may substantially compromise a woman's decision-making autonomy. Although welcome, it may not be effectively resistible. The UAGA's existing prohibition against the sale of human organs should be extended to protect fetal tissue donation from such controlling influences.

Could the altruistic thought of fetal tissue transplantation impose a controlling influence on a pregnant woman's decision about abortion? If a family member with diabetes or Parkinson's disease stands to benefit from a fetal tissue transplant, a woman might find reason to abandon fundamental beliefs against abortion. This effect may be real, but it is not coercive because the option of abortion is freely resistible and nonthreatening. There is one scenario, however, that could foster undue manipulation. If the woman were allowed to designate a specific person as the recipient of the transplant, the option of abortion may become effectively irresistible. In the case of permitting designated recipients, fetal tissue transplantation may be considered a substantially controlling influence over a woman's decision-making autonomy.

There must be safeguards in the donation process. First, financial incentives for fetal tissue donation should be declared explicitly illegal. Second, a woman should not be allowed to designate a specific recipient or group of transplanted tissue for her aborted fetus's tissue.

Ethical Dilemmas

Now that the scientific support, the political reality, and the ethical acceptability of fetal tissue transplantation have been established, new ethical issues arise. The Department of Health and Human Services will soon be creating guidelines and "safeguards" governing the use of fetal tissue. Many new questions must be addressed: How should fetal tissue be procured? Which transplant recipients should be given preference, and which diseases should be given preference? What type of informed consent ought to be obtained? Who should be responsible for obtaining informed consent from the tissue donors?

Managing Fetal Tissue

Tissue from an aborted human fetus deserves the same respect and dignity afforded tissue from an adult cadaver. A fetus possesses moral integrity, unlike blood or a kidney, and as such should be respected as a donor, not as a gift. By this definition, all fetal tissue donated for scientific research may be governed by the same ethical principles that govern the use of cadaveric organs.[33] In more than 95% of cases, an adult trauma victim, like a deceased fetus, contributes no direct consent to authorize organ donation. Instead, the UAGA designates the closest

relative, usually the parents of the deceased, to act as proxy for such consent. As such, any fetus whose death is unavoidable, as in the cases of spontaneous abortions and ectopic pregnancies, should be treated as would the body of a deceased adult.

Likewise in "avoidable" cases of elective abortion, fetal cadavers should be afforded the same dignity, neither more nor less, as that of adult cadavers. Indeed, some suggest that fetuses from elective abortions deserve greater protection from research use than do adult cadavers. Nolan extends this argument to conclude that fetuses from elective abortions should be ineligible as sources of transplantable tissue.[34] She argues that any woman who acts as an "agency of death" of a relative should not be able to act also as a decision-making proxy for that relative's organ donation. The fetus, in this model, is a murder victim, not an accident victim. Therefore, she suggests, only tissue from spontaneous abortions and ectopic pregnancies should be used in research.

To answer this argument, we must first understand that it is based on a moral opposition to the abortion procedure itself. It assumes that abortion is murder and that affording any authority to the murderer is wrong. The prevailing legal climate, however, "acquits" a woman choosing abortion of the charge of murder. Against that simple premise, the argument cannot stand.

But even if we accept the assumption that the fetus is a murder victim, the argument against the use of elective abortuses fails. Murder victims, like accident victims, are eligible organ donors under the provisions of the UAGA. The only prohibition, then, would be against asking the "agency of death" for consent. If the woman were to be viewed as a murderer, authority for donating tissue would rest in the hands of the nearest surviving relative—the woman's husband, the fetus's father, the woman's child—or, if one is neither available nor competent, authority would rest on a court order. The result (that each abortion require a search for the appropriate consenting adult) is absurd, but it does not prohibit the use of tissue from elective abortions. Instead, it makes the process cumbersome for clinicians and medicolegal staff, and it unjustly alienates women.

The UAGA, which has been active in most states since 1985, dictates guidelines for the treatment of any donated human tissue, including the following:

- No monetary compensation or services, including medical services, should be exchanged for donor tissue. The construed purpose of this guideline for fetal tissue transplantation is to protect a woman from undue manipulation during her decision to terminate a pregnancy.
- Informed consent should be obtained from the closest competent donor family member. By law, this gives the woman and the child's father equal power to authorize consent.

Under these guidelines, donors are allowed to designate recipients of donated organs, and the handling of donated tissue is not discussed. With this in mind, we recommend two additions to the guidelines established by the UAGA, designed specifically to address the sensitive issues of abortion and fetal tissue donation:

- The donor and donor family should be disconnected from the process of choosing the transplant recipient. As previously discussed, this prevents unjust consequences for recipients and undue influence on the donor families.
- Donor tissue should be acquired discreetly and rapidly. The most recent review of the literature indicates that the therapeutic function of grafted dopaminergic cells is greatest when the donor tissue is fresh.[35] Nonetheless, the tissue deserves the respect in handling that would be afforded any human cadaver. We recommend that each clinical facility providing donor fetal tissue include in its code a provision for Institutional Review Board oversight of fetal tissue procurement.

Selecting Recipients

The field of fetal tissue transplantation has yet to face a daunting obstacle that for years has complicated the field of adult organ transplantation: the inadequate supply of needed tissue. Current projections estimate the yearly incidence of elective abortions at about 1.5 million,[28] and the maximum estimate for the Parkinson's disease population of the United States is just under 510,000.[36] Should current experiments become remarkably successful with Parkinson's disease, the supply of transplantable tissue should be adequate. Furthermore, many researchers suggest a future in which one aborted fetus may be used to create multiple cell lines that have the potential to treat hundreds of patients. Nonetheless, if new protocols with other diseases prove fetal tissue transplantation useful in the treatment of larger patient populations such as those with diabetes or leukemia, the problem of rationing fetal tissue may become real.

Given that recipient populations for fetal tissue therapy are largely hypothetical, creating criteria now to help allocate donor tissue in the future is premature. Useful themes exist, however, in the current systems for choosing recipients of pediatric and adult organs. The process of organ procurement and allocation is orchestrated by the National Organ Procurement and Transplantation Network, established by Congress in 1984. Criteria to exclude possible recipients are social and medical: advanced age, inability to pay, lack of psychosocial support, psychiatric illness predisposing to noncompliance with a strict medical regimen, incompatible blood type, systemic infection, degree of organ failure, and a list of other medical conditions that varies with the type of transplantation. Ad hoc amendments to these criteria are often made, based on subjective judgments of social appropriateness or of the degree of medical emergency.[37] The social criteria are clearly the most ethically problematic, but they have withstood more than a decade of debate in the bioethics literature. These criteria can be debated on the same grounds regardless of the origin of the donated tissue.

Anticipating the arrival of fetal tissue transplantation

as a therapeutic reality, we suggest that any recipient selection scheme should include the following:

- A federal mandate to the National Organ Procurement and Transplantation Network to create a national registry of possible fetal tissue recipients.
- An annual conference of fetal tissue researchers, physicians, and surgeons to determine medical exclusion criteria specific to each of the newly approved therapies.
- The inclusion of bioethicists, psychiatrists, legal experts, and organ recipients in the annual conference to participate in the creation of exclusion criteria that are nonmedical.
- A prospective study of all fetal tissue recipients to accumulate data that will further inform the annual conference.

Requiring Informed Consent

Because a human fetus is more than a vestigial organ from the female body, researchers should not be allowed to acquire fetal tissue without a woman's consent. Under UAGA regulations, the fetus should be treated as donor and the pregnant woman as "next of kin." As already explained, the act of abortion does not disqualify her as an appropriate proxy for decision making regarding donation.

Under these definitions, informed consent for using fetal tissue in transplantation should be obtained from a pregnant woman before she has an elective abortion. Noting that the UAGA's definition of "next of kin" includes the father, the NIH advisory committee in 1988 added that fetal tissue should not be used if the father objects, "except in cases of incest or rape."[38] It is unnecessary, both from an ethical perspective and from a practical perspective, for researchers or transplant surgeons to obtain this consent in person. The best requester is a good communicator and counselor. In the area of cadaveric organ transplantation, the requester is usually a primary care physician, a primary care nurse, an emergency department physician, or an experienced liaison person from a local organ procurement organization. Similarly, fetal tissue researchers may opt to provide informed consent information through either physicians or an organ procurement organization. Once consent is obtained, the tissue should be removed from the operating suite by an authorized representative of the fetal tissue transplant team.

Informed consent should be requested only in cases in which there is a reasonable chance that the fetal tissue will be used for transplantation purposes. Given the currently low demand for such tissue, it would be unreasonable to require that all women seeking abortions be counseled about fetal tissue transplantation.

Ethics of Persuasion

Could the demand for fetal tissue encourage indirect inducements to abortion? As explained earlier, the supply of fetal tissue from elective abortions exceeds the current demand. But even if the demand increases dramatically, the feared inducements to increase abortion rates may likely be unsuccessful. After ten years of legal requirements and millions of dollars in educational efforts, the attempt to increase organ donation rates of adult donors has been largely unsuccessful. It is unlikely that less direct attempts to increase abortion rates would be more successful.

Even if successful, there is nothing morally wrong with providing information about fetal tissue transplants to influence a woman's decision making. This is the sort of rational portrayal of information that Faden and Beauchamp call persuasion.[31] Photographs of bloody fetuses have strong persuasive power, but their issuance to pregnant women contemplating abortions is not morally wrong. Similarly, the potential that tissue extracted from fetuses may improve the lives of persons with Parkinson's disease offers persuasive information that should not be peremptorily excluded from a woman's decision-making process.

One recently proposed piece of legislation threatened to limit such free exchange of information. Congressional bill HR 2507 explicitly exhorted a woman to identify the influences on her choice to have an abortion to ensure that fetal tissue transplantation is not one of those influences. The bill's language required physicians to be participants in this scrutiny.[23] Women get pregnant for many reasons, but no one suggests the need to monitor every woman's motivations to get pregnant. No legislator seriously proposes that pregnant women seen in publicly funded maternal health clinics sign documents attesting that their decision to have a child is "separate and independent" of economic, medical, or other external influences. Extending the same argument, no legislator should seriously propose to scrutinize a woman's decision-making process to terminate her pregnancy.

If the need for fetal tissue becomes as great as the current need for cadaveric organs, state governments may consider expanding the required request legislation to include women seeking abortions as a mandated population for organ donation requests. Persuading women to donate fetal tissue is not only ethically permissible, it may prove to be ethically necessary.

Suggested Guidelines for Fetal Tissue Transplantation

Based on the analysis of the ethical challenges to the use of fetal tissue, we suggest that fetal tissue transplantation is an ethically appropriate activity when subject to the following stipulations:

- Fetal tissue derived from dead fetuses resulting from elective abortions should be included under the principles of the Uniform Anatomical Gift Act.
- Financial incentives to a donor's family, physicians, researchers, or any other party involved in the donation of fetal tissue should be prohibited.
- Women donating fetal tissue should not be permitted to designate specific recipients of that tissue.
- Informed consent specific to the use of fetal tissue for research and transplantation should be made available to all women whose aborted fetuses may be used for the purposes of transplantation.

- Each clinical facility providing donor fetal tissue should mandate in its code Institutional Review Board oversight of fetal tissue procurement.
- The National Organ Procurement and Transplantation Network should include fetal tissue transplant recipients in its national registry.

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- Anorectal physiologic studies
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- Research activities including the physiology of continence and surgical techniques
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About the Director

Robert W. Beart, Jr., M.D., *Professor of Surgery at the USC School of Medicine, serves as Director of the USC Center for Colorectal Diseases. He is a world-renowned specialist in colon and rectal surgery, with extensive experience in performing and refining surgical alternatives to ileostomy and colostomy and laparoscopic colon resection.*

Dr. Beart received his medical degree from Harvard Medical School, and completed his internship and residencies at the University of Colorado Medical Center in Denver. He did a transplant fellowship (liver and kidney) at the University of Colorado, and a colon and rectal fellowship at the Mayo Clinic Rochester. For more than a decade, he served as Chairman, Colon and Rectal Surgery at the Mayo Clinic Rochester, and was named the Caywood Professor of Surgery. At the Mayo Clinic Scottsdale (Arizona), he was Chairman, Department of General Surgery. He joined USC University Hospital in 1992.

Dr. Beart, a member of numerous professional organizations, is the immediate Past President of the American Society of Colon and Rectal Surgeons. He is widely published in peer review journals, is the editor of Diseases of the Colon & Rectum, *and is a much sought after lecturer.*

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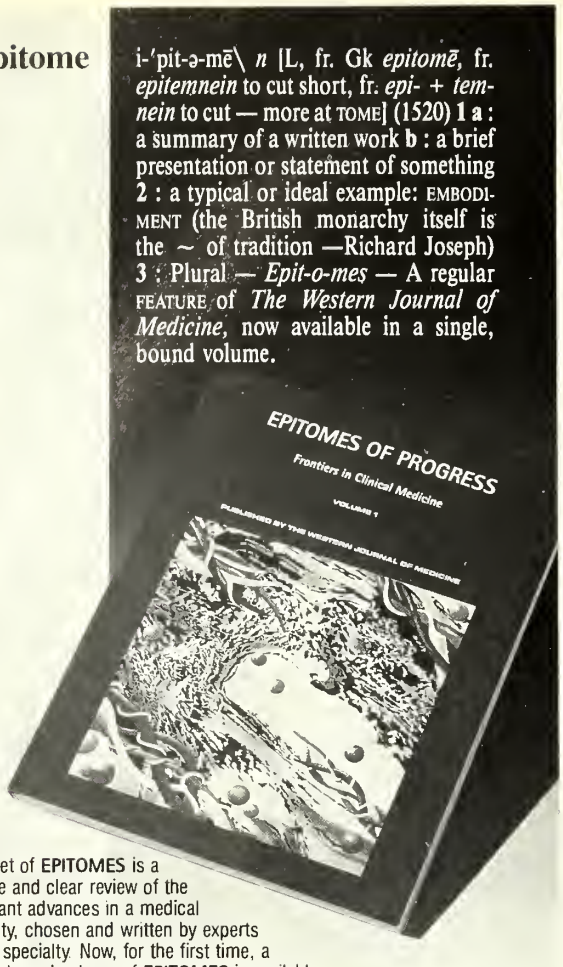

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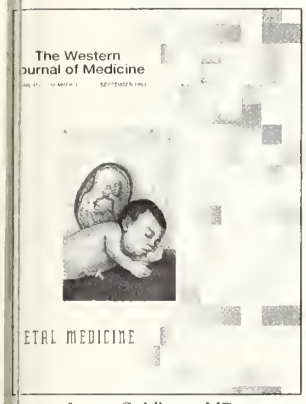

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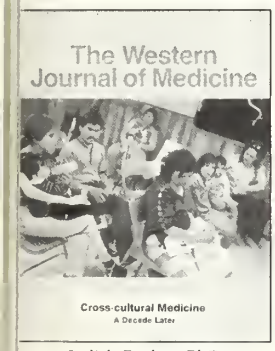

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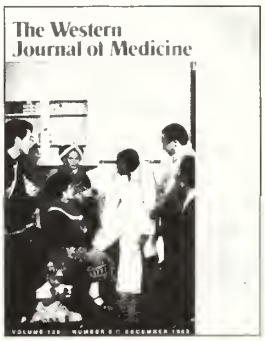

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ABSTRACTS SEPTEMBER 1993

(Lorenz HP, Adzick NS: Scarless skin wound repair in the fetus, *In* Fetal Medicine [Special Issue]. West J Med 1993; 159:350-355)

The ability of a fetus to heal without scar formation depends on its gestational age at the time of injury and the size of the wound defect. In general, linear incisions heal without scar until late in gestation whereas excisional wounds heal with scar at an earlier gestational age. The profiles of fetal proteoglycans, collagens, and growth factors are different from those in adult wounds. The less-differentiated state of fetal skin is probably an important characteristic responsible for scarless repair. There is minimal inflammation in fetal wounds. Fetal wounds are characterized by high levels of hyaluronic acid and its stimulator(s) with more rapid, highly organized collagen deposition. The roles of peptide growth factors such as transforming growth factor-β and basic fibroblast growth factor are less prominent in fetal than in adult wound healing. Platelet-derived growth factor has been detected in scarless fetal skin wounds, but its role is unknown. An understanding of scarless tissue repair has possible clinical application in the modulation of adult fibrotic diseases and abnormal scar-forming conditions.

FETAL SURGERY
SCARLESS TISSUE REPAIR
FETAL SKIN WOUNDS
WOUND REPAIR

(Lorenz HP, Adzick NS: Scarless skin wound repair in the fetus, *In* Fetal Medicine [Special Issue]. West J Med 1993; 159:350-355)

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WOUND REPAIR

(Lorenz HP, Adzick NS: Scarless skin wound repair in the fetus, *In* Fetal Medicine [Special Issue]. West J Med 1993; 159:350-355)

The ability of a fetus to heal without scar formation depends on its gestational age at the time of injury and the size of the wound defect. In general, linear incisions heal without scar until late in gestation whereas excisional wounds heal with scar at an earlier gestational age. The profiles of fetal proteoglycans, collagens, and growth factors are different from those in adult wounds. The less-differentiated state of fetal skin is probably an important characteristic responsible for scarless repair. There is minimal inflammation in fetal wounds. Fetal wounds are characterized by high levels of hyaluronic acid and its stimulator(s) with more rapid, highly organized collagen deposition. The roles of peptide growth factors such as transforming growth factor-β and basic fibroblast growth factor are less prominent in fetal than in adult wound healing. Platelet-derived growth factor has been detected in scarless fetal skin wounds, but its role is unknown. An understanding of scarless tissue repair has possible clinical application in the modulation of adult fibrotic diseases and abnormal scar-forming conditions.

FETAL SURGERY
SCARLESS TISSUE REPAIR
FETAL SKIN WOUNDS
WOUND REPAIR

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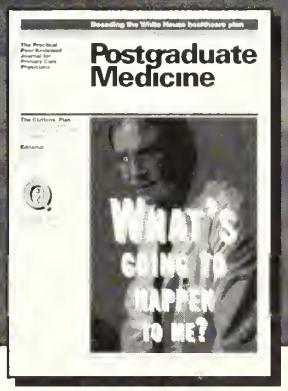

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(Continued on Page 416)

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(Continued on Page 419)

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(Continued from Page 418)

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(Continued on Page 420)

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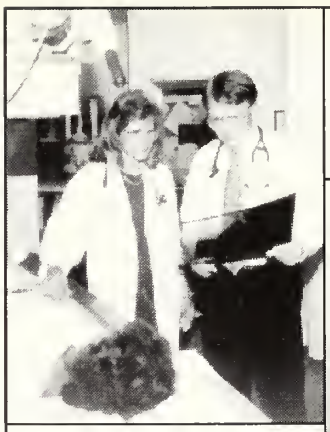

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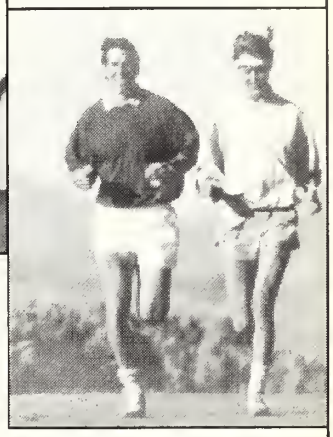

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(Continued from Page 419)

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(Continued on Page 421)

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California Medical Association–PO Box 7690, San Francisco 94120-7690. (415) 541-0900. Annual Meeting: March 18-23, 1994, Disneyland Hotel, Anaheim.

Colorado Medical Society–PO Box 17550, Denver 80217-0550. (303) 779-5455. Annual Meeting: 1994, date and location to be announced.

Hawaii Medical Association–1360 S Beretania, Honolulu 96814. (808) 536-7702. Annual Meeting: October 9-11, 1993, Ritz Carlton Kapalua, Maui.

Idaho Medical Association–305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888. Annual Meeting: 1994, date and location to be announced.

Montana Medical Association–2012 11th Ave, Suite 12, Helena 59601. (405) 443-4000. Annual Meeting: 1994, date and location to be announced.

Nevada State Medical Association–3660 Baker Lane, Reno 89502. (702) 825-6788. Annual Meeting: April 21-24, 1994, Coronado, California.

New Mexico Medical Society–7770 Jefferson NE, Suite 400, Albuquerque 87109. (505) 828-0237. Annual Meeting: 1994, date and location to be announced.

Utah Medical Association–540 E Fifth South, Salt Lake City 84102. (801) 355-7477. Annual Meeting: 1994, date and location to be announced.

Washington State Medical Association–900 United Airlines Bldg, 2033 6th Ave, Ste 1100, Seattle 98121. (206) 441-9762. Annual Meeting: 1994, date and location to be announced.

Wyoming Medical Society–PO Drawer 4009, Cheyenne 82003-4009. (307) 635-2424. Annual Meeting: 1994, date and location to be announced.

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For The Treatment Of Reflux Disease

WHEN ACID REFLUX ERUPTS

lac® 150 Tablets
itidine hydrochloride)
lac® 300 Tablets
itidine hydrochloride)
lac® Syrup
itidine hydrochloride)

BRIEF SUMMARY

following is a brief summary only Before prescribing, see complete prescribing information in ac® product labeling

ICATIONS AND USAGE: Zantac® is indicated in:
hort-term treatment of active duodenal ulcer
laintenance therapy for duodenal ulcer patients at reduced dosage after healing of acute ulcers
he treatment of pathological hypersecretory conditions (e.g., Zollinger-Ellison syndrome and sys-c mastocytosis)
hort-term treatment of active, benign gastric ulcer
reatment of gastroesophageal reflux disease (GERD)
reatment of endoscopically diagnosed erosive esophagitis.
oncomitant antacids should be given as needed for pain relief to patients with active duodenal ul-lactive, benign gastric ulcer, hypersecretory states, GERD, and erosive esophagitis.

TRAINOICATIONS: Zantac® is contraindicated for patients known to have hypersensitivity to the or any of the ingredients.

CAUTIONS: General: 1 Symptomatic response to Zantac® therapy does not preclude the pres-ot gastric malignancy.
ince Zantac is excreted primarily by the kidney, dosage should be adjusted in patients with im-ed renal function (see DOSAGE AND ADMINISTRATION). Caution should be observed in patients hepatic dysfunction since Zantac is metabolized in the liver
are reports suggest that Zantac may precipitate acute porphyric attacks in patients with acute por-ia. Zantac should therefore be avoided in patients with a history of acute porphyria
oratory Tests: False-positive tests for urine protein with Multistix® may occur during Zantac ther-and therefore testing with sulfosalicylic acid is recommended
Interactions: Although Zantac has been reported to bind weakly to cytochrome P-450 *in vitro*, mmended doses of the drug do not inhibit the action of the cytochrome P-450-linked oxygenase mes in the liver. However, there have been isolated reports of drug interactions that suggest that ac may affect the bioavailability of certain drugs by some mechanism as yet unidentified (e g , a lependent effect on absorption or a change in volume of distribution).
creased or decreased prothrombin times have been reported during concurrent use of ranitidine warfarin. However, in human pharmacokinetic studies with dosages of ranitidine up to 400 mg day, no interaction occurred, ranitidine had no effect on warfarin clearance or prothrombin time. possibility of an interaction with warfarin at dosages of ranitidine higher than 400 mg per day has een investigated
inogenesis, Mutagenesis, Impairment of Fertility: There was no indication of tumorigenic or inogenic effects in life-span studies in mice and rats at dosages up to 2,000 mg/kg per day
nitidine was not mutagenic in standard bacterial tests (*Salmonella, Escherichia coli*) for muta-city at concentrations up to the maximum recommended for these assays.
a dominant lethal assay, a single oral dose of 1,000 mg/kg to male rats was without effect on the ome of two matings per week for the next 9 weeks
nancy: ***Teratogenic Effects: Pregnancy Category B:*** Reproduction studies have been performed ts and rabbits at doses up to 160 times the human dose and have revealed no evidence of im-ed fertility or harm to the fetus due to Zantac There are, however, no adequate and well-controlled ies in pregnant women. Because animal reproduction studies are not always predictive of human onse, this drug should be used during pregnancy only if clearly needed
sing Mothers: Zantac is secreted in human milk Caution should be exercised when Zantac is ad-stered to a nursing mother.
atric Use: Safety and effectiveness in children have not been established
in Elderly Patients: Ulcer healing rates in elderly patients (65-82 years of age) were no different those in younger age-groups The incidence rates for adverse events and laboratory abnormali-were also not different from those seen in other age-groups.

ERSE REACTIONS: The following have been reported as events in clinical trials or in the routine agement of patients treated with Zantac® The relationship to Zantac therapy has been unclear in cases. Headache, sometimes severe, seems to be related to Zantac administration
ral Nervous System: Rarely, malaise, dizziness, somnolence, insomnia, and vertigo Rare cases versible mental confusion, agitation, depression, and hallucinations have been reported, predom-tly in severely ill elderly patients Rare cases of reversible blurred vision suggestive of a change in mmodation have been reported Rare reports of reversible involuntary motor disturbances have received
iovascular: As with other H_2-blockers, rare reports of arrhythmias such as tachycardia, brady-ia, atrioventricular block, and premature ventricular beats.
rointestinal: Constipation, diarrhea, nausea/vomiting, abdominal discomfort/pain, and rare re-s of pancreatitis.
atic: In normal volunteers, SGPT values were increased to at least twice the pretreatment levels in

Zantac® 150 and 300 (ranitidine hydrochloride) Tablets
Zantac® (ranitidine hydrochloride) Syrup

6 of 12 subjects receiving 100 mg q i d intravenously for 7 days, and in 4 of 24 subjects receiving 50 mg q i d intravenously for 5 days There have been occasional reports of hepatitis, hepatocellular or hepatocanalicular or mixed, with or without jaundice In such circumstances, ranitidine should be immediately discontinued These events are usually reversible, but in exceedingly rare circumstances death has occurred
Musculoskeletal: Rare reports of arthralgias and myalgias
Hematologic: Blood count changes (leukopenia, granulocytopenia, and thrombocytopenia) have occurred in a few patients These were usually reversible Rare cases of agranulocytosis, pancytopenia, sometimes with marrow hypoplasia, and aplastic anemia and exceedingly rare cases of acquired immune hemolytic anemia have been reported
Endocrine: Controlled studies in animals and man have shown no stimulation of any pituitary hormone by Zantac and no antiandrogenic activity, and cimetidine-induced gynecomastia and impotence in hypersecretory patients have resolved when Zantac has been substituted However, occasional cases of gynecomastia, impotence, and loss of libido have been reported in male patients receiving Zantac, but the incidence did not differ from that in the general population
Integumentary: Rash, including rare cases suggestive of mild erythema multiforme, and, rarely, alopecia
Other: Rare cases of hypersensitivity reactions (e g , bronchospasm, fever, rash, eosinophilia), anaphylaxis, angioneurotic edema, and small increases in serum creatinine

OVERDOSAGE: There has been limited experience with overdosage Reported acute ingestions of up to 18 g orally have been associated with transient adverse effects similar to those encountered in normal clinical experience (see ADVERSE REACTIONS) In addition, abnormalities of gait and hypotension have been reported

When overdosage occurs, the usual measures to remove unabsorbed material from the gastrointestinal tract, clinical monitoring, and supportive therapy should be employed

Studies in dogs receiving dosages of Zantac® in excess of 225 mg/kg per day have shown muscular tremors, vomiting, and rapid respiration Single oral doses of 1,000 mg/kg in mice and rats were not lethal Intravenous LD_{50} values in mice and rats were 77 and 83 mg/kg, respectively

OOSAGE AND ADMINISTRATION: (See complete prescribing information in Zantac® product labeling.)
Active Duodenal Ulcer: The current recommended adult oral dosage is 150 mg or 10 mL (2 teaspoonfuls equivalent to 150 mg of ranitidine) twice daily An alternative dosage of 300 mg or 20 mL (4 teaspoonfuls equivalent to 300 mg of ranitidine) once daily at bedtime can be used for patients in whom dosing convenience is important The advantages of one treatment regimen compared to the other in a particular patient population have yet to be demonstrated
Maintenance Therapy: The current recommended adult oral dosage is 150 mg or 10 mL (2 teaspoonfuls equivalent to 150 mg of ranitidine) at bedtime
Pathological Hypersecretory Conditions (such as Zollinger-Ellison syndrome): The current recommended adult oral dosage is 150 mg or 10 mL (2 teaspoonfuls equivalent to 150 mg of ranitidine) twice a day In some patients it may be necessary to administer Zantac® 150-mg doses more frequently Dosages should be adjusted to individual patient needs, and should continue as long as clinically indicated Dosages up to 6 g per day have been employed in patients with severe disease.
Benign Gastric Ulcer: The current recommended adult oral dosage is 150 mg or 10 mL (2 teaspoonfuls equivalent to 150 mg of ranitidine) twice a day
GERD: The current recommended adult oral dosage is 150 mg or 10 mL (2 teaspoonfuls equivalent to 150 mg of ranitidine) twice a day
Erosive Esophagitis: The current recommended adult oral dosage is 150 mg or 10 mL (2 teaspoonfuls equivalent to 150 mg of ranitidine) four times a day
Dosage Adjustment for Patients With Impaired Renal Function: On the basis of experience with a group of subjects with severely impaired renal function treated with Zantac, the recommended dosage in patients with a creatinine clearance less than 50 mL per minute is 150 mg or 10 mL (2 teaspoonfuls equivalent to 150 mg of ranitidine) every 24 hours Should the patient's condition require, the frequency of dosing may be increased to every 12 hours or even further with caution Hemodialysis reduces the level of circulating ranitidine Ideally, the dosing schedule should be adjusted so that the timing of a scheduled dose coincides with the end of hemodialysis

July 1992
2130B

Glaxo Pharmaceuticals
DIVISION OF GLAXO INC.

Zantac® 150 Tablets/Zantac® 300 Tablets.
Glaxo Pharmaceuticals, Research Triangle Park, NC 27709

Zantac® Syrup
Manufactured for Glaxo Pharmaceuticals, Research Triangle Park, NC 27709
by Roxane Laboratories, Inc., Columbus, OH 43216

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Zantac® Tablets

ranitidine HCl/Glaxo 150 mg tablets bid

For The Treatment Of Reflux Disease

WHEN ACID REFLUX ERUPTS

Please see Brief Summary of Prescribing Information on adjacent page.

Glaxo/ Roche

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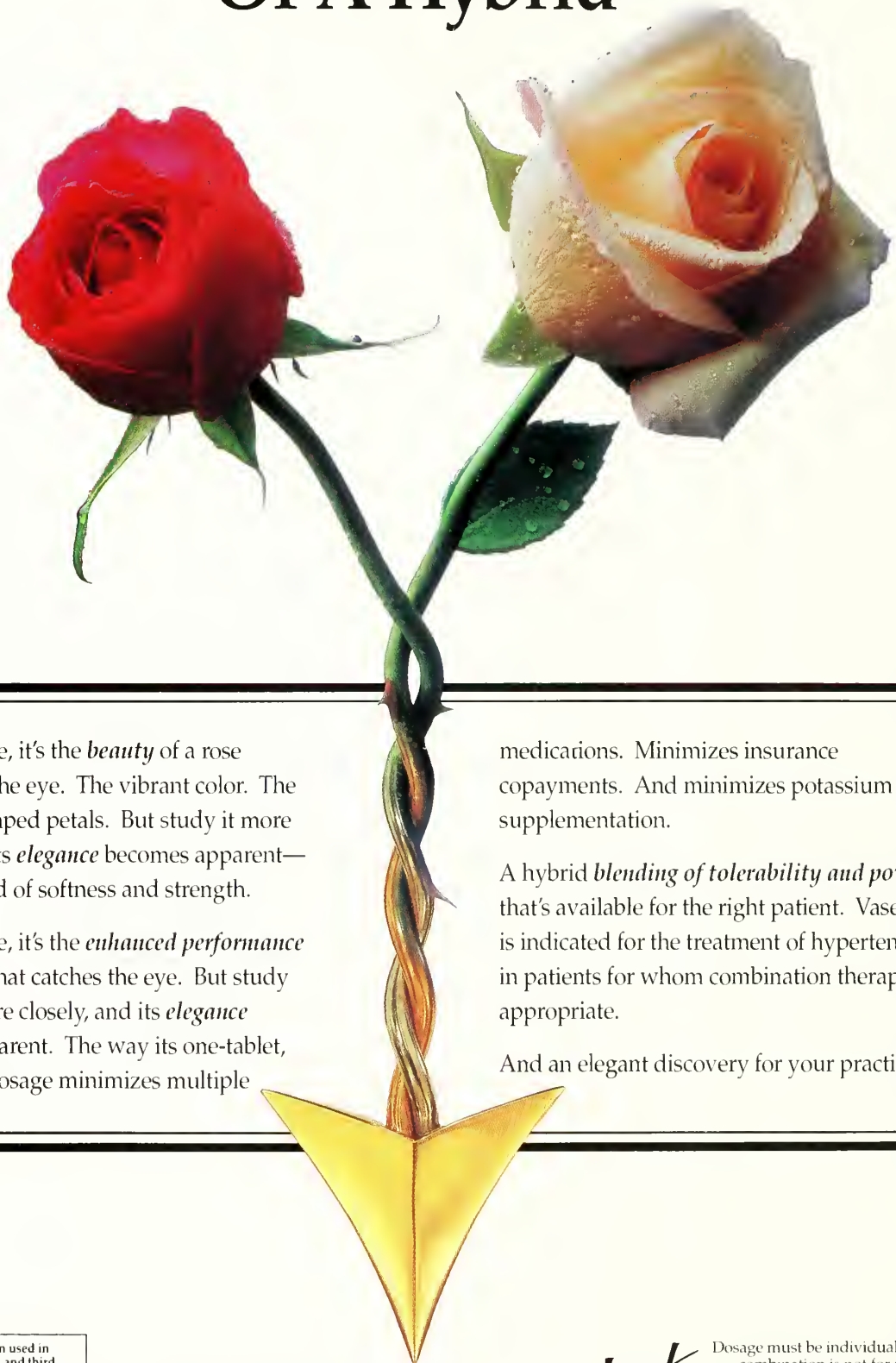
Second Class

Discover The Elegance Of A Hybrid



At first glance, it's the ***beauty*** of a rose that catches the eye. The vibrant color. The delicately shaped petals. But study it more closely, and its ***elegance*** becomes apparent—a gentle blend of softness and strength.

At first glance, it's the ***enhanced performance*** of Vaseretic that catches the eye. But study Vaseretic more closely, and its ***elegance*** becomes apparent. The way its one-tablet, once-a-day dosage minimizes multiple medications. Minimizes insurance copayments. And minimizes potassium supplementation.

A hybrid ***blending of tolerability and power*** that's available for the right patient. Vaseretic is indicated for the treatment of hypertension in patients for whom combination therapy is appropriate.

And an elegant discovery for your practice.

USE IN PREGNANCY: When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, Vaseretic® (Enalapril Maleate-Hydrochlorothiazide) should be discontinued as soon as possible. See WARNINGS, *Fetal/Neonatal Morbidity and Mortality.*

VASERETIC® 10-25 *Next*
Enalapril Maleate-Hydrochlorothiazide

Dosage must be individualized; the fixed combination is not for initial therapy.

Evaluation of the hypertensive patient should always include assessment of renal function.

For a Brief Summary of Prescribing Information, see adjacent pages.

TABLETS
VASERETIC®
(ENALAPRIL MALEATE-HYDROCHLOROTHIAZIDE)

USE IN PREGNANCY: When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, VASERETIC® (Enalapril Maleate-Hydrochlorothiazide) should be discontinued as soon as possible. See WARNINGS, *Fetal/Neonatal Morbidity and Mortality*

CONTRAINDICATIONS: VASERETIC is contraindicated in patients who are hypersensitive to any component of this product and in patients with a history of angioedema related to previous treatment with an angiotensin converting enzyme inhibitor. Because of the hydrochlorothiazide component, this product is contraindicated in patients with anuria or hypersensitivity to other sulfonamide-derived drugs.

WARNINGS: *General; Enalapril Maleate; Hypotension:* Excessive hypotension was rarely seen in uncomplicated hypertensive patients but is a possible consequence of enalapril use in severely salt/volume depleted persons such as those treated vigorously with diuretics or patients on dialysis.

Syncope has been reported in 1-3 percent of patients receiving VASERETIC. In patients receiving enalapril alone, the incidence of syncope is 0.5 percent. The overall incidence of syncope may be reduced by proper titration of the individual components. (See PRECAUTIONS, *Drug Interactions*, and ADVERSE REACTIONS.)

In patients with severe congestive heart failure, with or without associated renal insufficiency, excessive hypotension has been observed and may be associated with oliguria and/or progressive azotemia, and rarely with acute renal failure and/or death. Because of the potential fall in blood pressure in these patients, therapy should be started under very close medical supervision. Such patients should be followed closely for the first two weeks of treatment and whenever the dose of enalapril and/or diuretic is increased. Similar considerations may apply to patients with ischemic heart or cerebrovascular disease, in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident.

If hypotension occurs, the patient should be placed in the supine position and, if necessary, receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses, which usually can be given without difficulty once the blood pressure has increased after volume expansion.

Angioedema: Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported in patients treated with angiotensin converting enzyme inhibitors, including enalapril. In such cases VASERETIC should be promptly discontinued and appropriate therapy and monitoring should be provided until complete and sustained resolution of signs and symptoms has occurred. In instances where swelling has been confined to the face and lips the condition has generally resolved without treatment, although antihistamines have been useful in relieving symptoms. Angioedema associated with laryngeal edema may be fatal. **Where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, appropriate therapy, e.g., subcutaneous epinephrine solution 1:1000 (0.3 mL to 0.5 mL) and/or measures necessary to ensure a patent airway, should be promptly provided.** (See ADVERSE REACTIONS.)

Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor (see also CONTRAINDICATIONS).

Neutropenia/Agranulocytosis: Another angiotensin converting enzyme inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression, rarely in uncomplicated patients but more frequently in patients with renal impairment especially if they also have a collagen vascular disease. Available data from clinical trials of enalapril are insufficient to show that enalapril does not cause agranulocytosis at similar rates. Marketing experience has revealed several cases of neutropenia or agranulocytosis in which a causal relationship to enalapril cannot be excluded. Periodic monitoring of white blood cell counts in patients with collagen vascular disease and renal disease should be considered.

Hydrochlorothiazide: Thiazides should be used with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. Cumulative effects of the drug may develop in patients with impaired renal function.

Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.

Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma.

The possibility of exacerbation or activation of systemic lupus erythematosus has been reported.

Lithium generally should not be given with thiazides (see PRECAUTIONS, *Drug Interactions, Enalapril Maleate and Hydrochlorothiazide*).

Pregnancy; Enalapril-Hydrochlorothiazide: There was no teratogenicity in rats given up to 90 mg/kg/day of enalapril (150 times the maximum human dose) in combination with 10 mg/kg/day of hydrochlorothiazide (2 1/2 times the maximum human dose) or in mice given up to 30 mg/kg/day of enalapril (50 times the maximum human dose) in combination with 10 mg/kg/day of hydrochlorothiazide (2 1/2 times the maximum human dose). At these doses, fetotoxicity expressed as a decrease in average fetal weight occurred in both species. No fetotoxicity occurred at lower doses; 30/10 mg/kg/day of enalapril-hydrochlorothiazide in rats and 10/10 mg/kg/day of enalapril-hydrochlorothiazide in mice.

When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, VASERETIC should be discontinued as soon as possible. (See *Enalapril Maleate; Fetal/Neonatal Morbidity and Mortality*, below.)

Enalapril Maleate; Fetal/Neonatal Morbidity and Mortality: ACE inhibitors can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature. When pregnancy is detected, ACE inhibitors should be discontinued as soon as possible.

The use of ACE inhibitors during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to the ACE-inhibitor exposure.

These adverse effects do not appear to have resulted from intrauterine ACE-inhibitor exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to ACE inhibitors only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should make every effort to discontinue the use of VASERETIC as soon as possible.

Rarely (probably less often than once in every thousand pregnancies), no alternative to ACE inhibitors will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intraamniotic environment.

If oligohydramnios is observed, VASERETIC should be discontinued unless it is considered lifesaving for the mother. Contraction stress testing (CST), a non-stress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of *in utero* exposure to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function. Enalaprilat, which crosses the placenta, has been removed from neonatal circulation by peritoneal dialysis with some clinical benefit, and theoretically may be removed by exchange transfusion, although there is no experience with the latter procedure.

No teratogenic effects of enalapril were seen in studies of pregnant rats and rabbits. On a mg/kg basis, the doses used were up to 333 times (in rats), and 50 times (in rabbits) the maximum recommended human dose.

Hydrochlorothiazide, Teratogenic Effects: Reproduction studies in the rabbit, the mouse and the rat at doses up to 100 mg/kg/day (50 times the human dose) showed no evidence of external abnormalities of the fetus due to hydrochlorothiazide. Hydrochlorothiazide given in a two-litter study in rats at doses of 4-5.6 mg/kg/day (approximately 1-2 times the usual daily human dose) did not impair fertility or produce birth abnormalities in the offspring. Thiazides cross the placental barrier and appear in cord blood.

Nonteratogenic Effects: These may include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult.

PRECAUTIONS: *General; Enalapril Maleate; Impaired Renal Function:* As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe congestive heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with angiotensin converting enzyme inhibitors, including enalapril, may be associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death.

In clinical studies in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine were observed in 20 percent of patients. These increases were almost always reversible upon discontinuation of enalapril and/or diuretic therapy. In such patients renal function should be monitored during the first few weeks of therapy.

Some patients with hypertension or heart failure with no apparent pre-existing renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when enalapril has been given concomitantly with a diuretic. This is more likely to occur in patients with pre-existing renal impairment. Dosage reduction of enalapril and/or discontinuation of the diuretic may be required.

Evaluation of the hypertensive patient should always include assessment of renal function.

Hemodialysis Patients: Anaphylactoid reactions have been reported in patients dialyzed with high-flux membranes (e.g., AN 69*) and treated concomitantly with an ACE inhibitor. In these patients consideration should be given to using a different type of dialysis membrane or a different class of antihypertensive agent.

Hyperkalemia: Elevated serum potassium (greater than 5.7 mEq/L) was observed in approximately one percent of hypertensive patients in clinical trials treated with enalapril alone. In most cases these were isolated values which resolved despite continued therapy, although hyperkalemia was a cause of discontinuation of therapy in 0.28 percent of hypertensive patients. Hyperkalemia was less frequent (approximately 0.1 percent) in patients treated with enalapril plus hydrochlorothiazide. Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with enalapril. (See *Drug Interactions*.)

Cough: Cough has been reported with the use of ACE inhibitors. Characteristically, the cough is nonproductive, persistent and resolves after discontinuation of therapy. ACE inhibitor-induced cough should be considered as part of the differential diagnosis of cough.

Surgery/Anesthesia: In patients undergoing major surgery or during anesthesia with agents that produce hypotension, enalapril may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Hydrochlorothiazide: Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals. All patients receiving thiazide therapy should be observed for clinical signs of fluid or electrolyte imbalance: hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Warning signs or symptoms of fluid and electrolyte imbalance, irrespective of cause, include dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, confusion, seizures, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting.

Hypokalemia may develop, especially with brisk diuresis, when severe cirrhosis is present, or after prolonged therapy. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Hypokalemia may cause cardiac arrhythmia and may also sensitize or exaggerate the response of the heart to the toxic effects of digitalis (e.g., increased ventricular irritability). Because enalapril reduces the production of aldosterone, concomitant therapy with enalapril attenuates the diuretic-induced potassium loss (see *Drug Interactions, Agents Increasing Serum Potassium*).

Although any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease), chloride replacement may be required in the treatment of metabolic alkalosis.

Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction, rather than administration of salt except in rare instances when the hyponatremia is life-threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Hyperuricemia may occur or frank gout may be precipitated in certain patients receiving thiazide therapy.

In diabetic patients dosage adjustments of insulin or oral hypoglycemic agents may be required. Hyperglycemia may occur with thiazide diuretics. Thus latent diabetes mellitus may become manifest during thiazide therapy.

The antihypertensive effects of the drug may be enhanced in the postsympathectomy patient.

If progressive renal impairment becomes evident consider withholding or discontinuing diuretic therapy.

Thiazides have been shown to increase the urinary excretion of magnesium, this may result in hypomagnesemia.

Thiazides may decrease urinary calcium excretion. Thiazides may cause intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

Increases in cholesterol and triglyceride levels may be associated with thiazide diuretic therapy.

Information for Patients; Angioedema: Angioedema, including laryngeal edema, may occur especially following the first dose of enalapril. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, extremities, eyes, lips, tongue, difficulty in swallowing or breathing) and to take no more drug until they have consulted with the prescribing physician.

Hypotension: Patients should be cautioned to report lightheadedness especially during the first few days of therapy. If actual syncope occurs, the patients should be told to discontinue the drug until they have consulted with the prescribing physician.

All patients should be cautioned that excessive perspiration and dehydration may lead to an excessive fall in blood pressure because of reduction in fluid volume. Other causes of volume depletion such as vomiting or diarrhea may also lead to a fall in blood pressure; patients should be advised to consult with the physician.

Hyperkalemia: Patients should be told not to use salt substitutes containing potassium without consulting their physician.

Neutropenia: Patients should be told to report promptly any indication of infection (e.g., sore throat, fever) which may be a sign of neutropenia.

Pregnancy: Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to ACE inhibitors, and they should also be told that these consequences do not appear to have resulted from intrauterine ACE-inhibitor exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.

NOTE: As with many other drugs, certain advice to patients being treated with VASERETIC is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Drug Interactions; Enalapril Maleate; Hypotension—Patients on Diuretic Therapy: Patients on diuretics and especially those in whom diuretic therapy was recently instituted, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with enalapril. The possibility of hypotensive effects with enalapril can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with enalapril. If it is necessary to continue the diuretic, provide medical supervision for at least two hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS.)

Agents Causing Renin Release: The antihypertensive effect of enalapril is augmented by antihypertensive agents that cause renin release (e.g., diuretics).

Other Cardiovascular Agents: Enalapril has been used concomitantly with beta adrenergic-blocking agents, methyldopa, nitrates, calcium-blocking agents, hydralazine and prazosin without evidence of clinically significant adverse interactions.

Agents Increasing Serum Potassium: Enalapril attenuates diuretic-induced potassium loss. Potassium-sparing diuretics (e.g., spironolactone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium. Therefore, if concomitant use of these agents is indicated because of demonstrated hypokalemia they should be used with caution and with frequent monitoring of serum potassium.

Lithium: Lithium toxicity has been reported in patients receiving lithium concomitantly with drugs which cause elimination of sodium, including ACE inhibitors. A few cases of lithium toxicity have been reported in patients receiving concomitant enalapril and lithium and were reversible upon discontinuation of both drugs. It is recommended that serum lithium levels be monitored frequently if enalapril is administered concomitantly with lithium.

Hydrochlorothiazide: When administered concurrently the following drugs may interact with thiazide diuretics:

Alcohol, barbiturates, or narcotics—potentiation of orthostatic hypotension may occur.

Antidiabetic drugs (oral agents and insulin)—dosage adjustment of the antidiabetic drug may be required.

Other antihypertensive drugs—additive effect or potentiation.

Cholestyramine and colestipol resins—Cholestyramine and colestipol resins bind the hydrochlorothiazide and reduce its absorption from the gastrointestinal tract by up to 85 and 43 percent, respectively. Thiazides may be administered two to four hours before the resin when the two drugs are used concomitantly.

Corticosteroids, ACTH—intensified electrolyte depletion, particularly hypokalemia.

Pressor amines (e.g., norepinephrine)—possible decreased response to pressor amines but not sufficient to preclude their use.

Skeletal muscle relaxants, nondepolarizing (e.g., tubocurarine)—possible increased responsiveness to the muscle relaxant.

Lithium—should not generally be given with diuretics. Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity. Refer to the package insert for lithium preparations before use of such preparations with VASERETIC.

Non-steroidal Anti-inflammatory Drugs—In some patients, the administration of a non-steroidal anti-inflammatory agent can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing and thiazide diuretics. Therefore, when VASERETIC and non-steroidal anti-inflammatory agents are used concomitantly, the patient should be observed closely to determine if the desired effect of the diuretic is obtained.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Enalapril in combination with hydrochlorothiazide was not mutagenic in the Ames microbial mutagen test with or without metabolic activation. Enalapril-hydrochlorothiazide did not produce DNA single strand breaks in an *in vitro* alkaline elution assay in rat hepatocytes or chromosomal aberrations in an *in vivo* mouse

10 mg

25 mg

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bone marrow assay

Enalapril Maleate: There was no evidence of a tumorigenic effect when enalapril was administered for 106 weeks to rats at doses up to 90 mg/kg/day (150 times* the maximum daily human dose). Enalapril has also been administered for 94 weeks to male and female mice at doses up to 90 and 180 mg/kg/day, respectively, (150 and 300 times* the maximum daily dose for humans) and showed no evidence of carcinogenicity.

Neither enalapril maleate nor the active diacid was mutagenic in the Ames microbial mutagen test with or without metabolic activation. Enalapril was also negative in the following genotoxicity studies: rec-assay, reverse mutation assay with *E. coli*, sister chromatid exchange with cultured mammalian cells, and the micronucleus test with mice, as well as in an *in vivo* cytogenic study using mouse bone marrow.

There were no adverse effects on reproductive performance in male and female rats treated with 10 to 90 mg/kg/day of enalapril.

Hydrochlorothiazide: Two-year feeding studies in mice and rats conducted under the auspices of the National Toxicology Program (NTP) uncovered no evidence of a carcinogenic potential of hydrochlorothiazide in female mice (at doses of up to approximately 600 mg/kg/day) or in male and female rats (at doses of up to approximately 100 mg/kg/day). The NTP, however, found equivocal evidence for hepatocarcinogenicity in male mice.

Hydrochlorothiazide was not genotoxic *in vitro* in the Ames mutagenicity assay of *Salmonella typhimurium* strains TA 98, TA 100, TA 1535, TA 1537, and TA 1538 and in the Chinese Hamster Ovary (CHO) test for chromosomal aberrations, or *in vivo* in assays using mouse germinal cell chromosomes, Chinese hamster bone marrow chromosomes, and the *Drosophila* sex-linked recessive lethal trait gene. Positive test results were obtained only in the *in vitro* CHO Sister Chromatid Exchange (clastogenicity) and in the Mouse Lymphoma Cell (mutagenicity) assays, using concentrations of hydrochlorothiazide from 43 to 1300 µg/mL, and in the *Aspergillus nidulans* non-disjunction assay at an unspecified concentration.

Hydrochlorothiazide had no adverse effects on the fertility of mice and rats of either sex in studies wherein these species were exposed, via their diet, to doses of up to 100 and 4 mg/kg, respectively, prior to conception and throughout gestation.

Pregnancy, Pregnancy Categories C (first trimester) *and D* (second and third trimesters). See WARNINGS, *Pregnancy, Enalapril Maleate, Fetal/Neonatal Morbidity and Mortality.*

Nursing Mothers: Enalapril and enalaprilat are detected in human milk in trace amounts. Thiazides do appear in human milk. Because of the potential for serious reactions in nursing infants from either drug, a decision should be made whether to discontinue nursing or to discontinue VASERETIC, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: VASERETIC has been evaluated for safety in more than 1500 patients, including over 300 patients treated for one year or more. In clinical trials with VASERETIC no adverse experiences peculiar to this combination drug have been observed. Adverse experiences that have occurred, have been limited to those that have been previously reported with enalapril or hydrochlorothiazide.

The most frequent clinical adverse experiences in controlled trials were: dizziness (8.6 percent), headache (5.5 percent), fatigue (3.9 percent) and cough (3.5 percent). Adverse experiences occurring in greater than two percent of patients treated with VASERETIC in controlled clinical trials were: muscle cramps (2.7 percent), nausea (2.5 percent), asthenia (2.4 percent), orthostatic effects (2.3 percent), impotence (2.2 percent), and diarrhea (2.1 percent).

Clinical adverse experiences occurring in 0.5 to 2.0 percent of patients in controlled trials included. *Body As A Whole:* Syncope, chest pain, abdominal pain; *Cardiovascular:* Orthostatic hypotension, palpitation, tachycardia; *Digestive:* Vomiting, dyspepsia, constipation, flatulence, dry mouth; *Nervous/Psychiatric:* Insomnia, nervousness, paresthesia, somnolence, vertigo; *Skin:* Pruritus, rash; *Other:* Dyspnea, gout, back pain, arthralgia, diaphoresis, decreased libido, tinnitus, urinary tract infection.

Angioedema: Angioedema has been reported in patients receiving VASERETIC (0.6 percent). Angioedema associated with laryngeal edema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis and/or larynx occurs, treatment with VASERETIC should be discontinued and appropriate therapy instituted immediately. (See WARNINGS.)

Hypotension: In clinical trials, adverse effects relating to hypotension occurred as follows: hypotension (0.9 percent), orthostatic hypotension (1.5 percent), other orthostatic effects (2.3 percent). In addition syncope occurred in 1.3 percent of patients. (See WARNINGS.)

Cough: See PRECAUTIONS, *Cough.*

Clinical Laboratory Test Findings; Serum Electrolytes: See PRECAUTIONS.

Creatinine, Blood Urea Nitrogen: In controlled clinical trials minor increases in blood urea nitrogen and serum creatinine, reversible upon discontinuation of therapy, were observed in about 0.6 percent of patients with essential hypertension treated with VASERETIC. More marked increases have been reported in other enalapril experience. Increases are more likely to occur in patients with renal artery stenosis. (See PRECAUTIONS.)

Serum Uric Acid, Glucose, Magnesium, and Calcium: See PRECAUTIONS.

Hemoglobin and Hematocrit: Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.3 g percent and 1.0 vol percent, respectively) occur frequently in hypertensive patients treated with VASERETIC but are rarely of clinical importance unless another cause of anemia coexists. In clinical trials, less than 0.1 percent of patients discontinued therapy due to anemia.

Liver Function Tests: Rarely, elevations of liver enzymes and/or serum bilirubin have occurred.

Other adverse reactions that have been reported with the individual components are listed below and, within each category, are in order of decreasing severity.

Enalapril Maleate—Enalapril has been evaluated for safety in more than 10,000 patients. In clinical trials adverse reactions which occurred with enalapril were also seen with VASERETIC. However, since enalapril has been marketed, the following adverse reactions have been reported. *Body As A Whole:* Anaphylactoid reactions (see PRECAUTIONS, *Hemodialysis Patients*); *Cardiovascular:* Cardiac arrest, myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high risk patients (see WARNINGS, *Hypotension*), pulmonary embolism and infarction; pulmonary edema, rhythm disturbances including atrial tachycardia and bradycardia, atrial fibrillation, hypotension; angina pectoris; *Digestive:* Ileus, pancreatitis, hepatic failure, hepatitis (hepatocellular [proven on rechallenge] or cholestatic jaundice), melena, anorexia, glossitis, stomatitis, dry mouth; *Hematologic:* Rare cases of neutropenia, thrombocytopenia and bone marrow depression, a few cases of hemolysis in patients with G-6-PD deficiency have been reported in which a causal relationship to enalapril cannot be excluded; *Nervous System/Psychiatric:* Depression, confusion, ataxia, peripheral neuropathy (e.g., paresthesia, dysesthesia); *Urogenital:* Renal failure, oliguria, renal dysfunction (see PRECAUTIONS), flank pain, gynecomastia; *Respiratory:* Pulmonary infiltrates, bronchospasm, pneumonia, bronchitis, rhinorrhea, sore throat and hoarseness, asthma, upper respiratory infection; *Skin:* Exfoliative dermatitis, toxic epidermal necrolysis, Stevens-Johnson syndrome, herpes zoster, erythema multiforme, urticaria, alopecia, flushing, photosensitivity; *Special Senses:* Blurred vision, taste alteration, anosmia, conjunctivitis, dry eyes, tearing.

Miscellaneous: A symptom complex has been reported which may include a positive ANA, an elevated erythrocyte sedimentation rate, arthralgia/arthritis, myalgia, fever, serositis, vasculitis, leukocytosis, eosinophilia, photosensitivity, rash and other dermatologic manifestations.

Fetal/Neonatal Morbidity and Mortality: See WARNINGS, *Pregnancy, Enalapril Maleate, Fetal/Neonatal Morbidity and Mortality.*

Hydrochlorothiazide—Body as a Whole: Weakness; *Digestive:* Pancreatitis, jaundice (intrahepatic cholestatic jaundice), sialadenitis, cramping, gastric irritation, anorexia; *Hematologic:* Aplastic anemia, agranulocytosis, leukopenia, hemolytic anemia, thrombocytopenia; *Hypersensitivity:* Purpura, photosensitivity, urticaria, necrotizing angiitis (vasculitis and cutaneous vasculitis), fever, respiratory distress including pneumonitis and pulmonary edema, anaphylactic reactions; *Musculoskeletal:* Muscle spasm; *Nervous System/Psychiatric:* Restlessness; *Renal:* Renal failure, renal dysfunction, interstitial nephritis (see WARNINGS); *Skin:* Erythema multiforme including Stevens-Johnson syndrome, exfoliative dermatitis including toxic epidermal necrolysis, alopecia; *Special Senses:* Transient blurred vision, xanthopsia.

* Based on patient weight of 50 kg.

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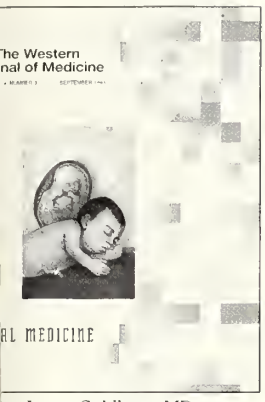

James Goldberg, MD
Special Issue Editor, 1993

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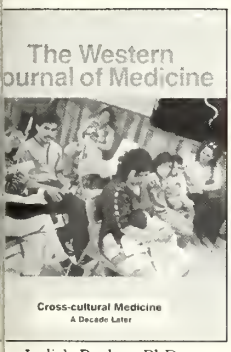

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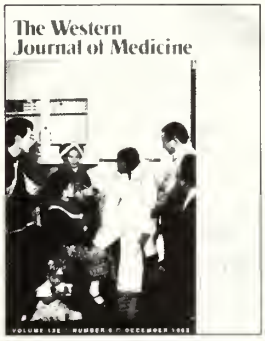

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1. A. Morales et al., New England Journal of Medicine: 1221. November 12, 1981.
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4. A. Morales et al., The Journal of Urology 128: 45-47, 1982.

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A CASE STUDY

A 38-year-old male presented with a chronic osteomyelitis with nonunion and bone loss following an open fracture of his distal tibia and ankle. The patient had previous internal fixation with a plate.

The patient was treated by Dr. Michael Patzakis with surgical debridement of all necrotic tissue and bone, and removal of internal fixation and placement of an external fixator. Four days later, the patient had a free vascularized rectus abdominis muscle transfer performed by Dr. Randy Sherman, plastic surgeon. Antibiotic therapy was under the direction of Dr. Paul Holtom, infectious disease consultant.

The patient subsequently was bone grafted by Dr. Patzakis due to a 2-inch bone defect and nonunion. At six months, the patient's fracture was healed and he was ambulating. He returned to work 10½ months after undergoing vocational rehabilitation and remains infection free with an excellent functional result.

Michael J. Patzakis, M.D., professor and chairman of Orthopaedics at the USC School of Medicine and director of the USC Orthopaedic Infection Service has arrested infection in many of his patients with chronic osteomyelitis using several new treatment modalities.

Dr. Patzakis joined the USC School of Medicine faculty in 1969 after holding an academic post at the University of Colorado, where he previously completed his fellowship in rheumatoid surgery. He earned his medical degree from Ohio State University, and completed his orthopaedic residency at Los Angeles County+USC Medical Center. He is a member of numerous professional organizations, and in 1991 served as president-elect of the International Muscular Skeletal Infection Society.

The Center's multidisciplinary team, faculty of the USC School of Medicine is recognized for its clinical expertise in the treatment of osteomyelitis, infected non-unions of bones, infected total joints, bone reconstruction and muscle and microvascular soft tissue transfers. The team is led by Dr. Patzakis, who has earned an international reputation for his clinical expertise in orthopaedic infections, osteomyelitis and septic arthritis. He specializes in the treatment of orthopaedic infections, in association with Randy Sherman, M.D., who specializes in plastic and microvascular surgery; and, Jackson Lee, M.D., whose specialty is orthopaedic trauma.

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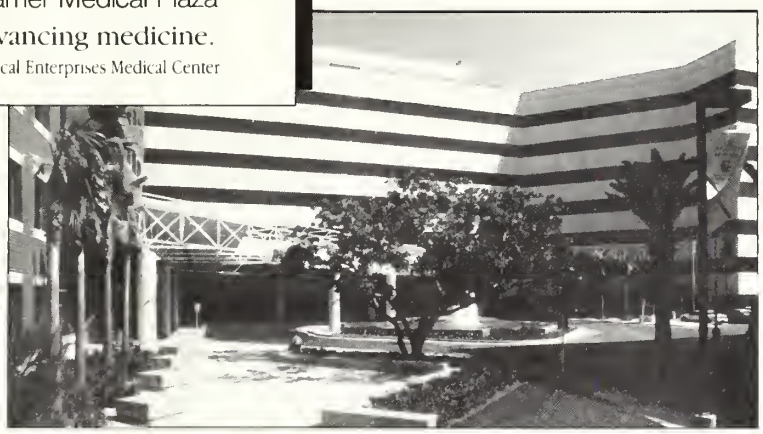

Because of treatments including more potent antibiotics and aggressive surgical approaches such as bone grafting, soft tissue transfers and revascularization techniques, it is now possible to achieve arrest in many infections that previously led to amputations or were considered incurable.

The beads shown above resemble a string of pearls, but in fact are actually antibiotic-impregnated beads — a new weapon in the ongoing fight against bone infection. The chain of antibiotic beads are surgically placed within the area of the infected bone or joint, allowing the antibiotic to leach out into the surrounding tissues.

Although infections occur in only approximately one percent of all orthopaedic operations, the large numbers of these surgeries performed nationwide result in thousands of bone infection cases each year. The majority of infections treated by the USC Infection Service are those resulting from trauma, hematogenous spread, or following surgery. Specialties include:

Reconstructive Microvascular Surgery

• Successful complex wound management is crucial to patients with orthopaedic infections. The addition of healthy vascularized soft tissue, obliteration of dead space, and closure of wounds without tension plays a central role in a high cure rate, as does a large experience in myocutaneous flap and microvascular surgery.

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The Western Journal of Medicine

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EPITOMES—IMPORTANT ADVANCES IN CLINICAL MEDICINE

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BRIEF SUMMARY

Contraindications: Severe LV dysfunction (see *Warnings*), hypotension (systolic pressure < 90 mm Hg) or cardiogenic shock, sick sinus syndrome (if no pacemaker is present), 2nd- or 3rd-degree AV block (if no pacemaker is present), atrial flutter/fibrillation with an accessory bypass tract (eg, WPW or LGL syndromes), hypersensitivity to verapamil.

Warnings: Verapamil should be avoided in patients with severe LV dysfunction (eg, ejection fraction < 30%) or moderate to severe symptoms of cardiac failure and in patients with any degree of ventricular dysfunction if they are receiving a beta-blocker. Control milder heart failure with optimum digitalization and/or diuretics before Calan SR is used. Verapamil may occasionally produce hypotension. Elevations of liver enzymes have been reported. Several cases have been demonstrated to be produced by verapamil. Periodic monitoring of liver function in patients on verapamil is prudent. Some patients with paroxysmal and/or chronic atrial flutter/fibrillation and an accessory AV pathway (eg, WPW or LGL syndromes) have developed an increased antegrade conduction across the accessory pathway bypassing the AV node, producing a very rapid ventricular response or ventricular fibrillation after receiving I.V. verapamil (or digitalis). Because of this risk, oral verapamil is contraindicated in such patients. AV block may occur (2nd- and 3rd-degree, 0.8%). Development of marked 1st-degree block or progression to 2nd- or 3rd-degree block requires reduction in dosage or, rarely, discontinuation and institution of appropriate therapy. Sinus bradycardia, 2nd-degree AV block, sinus arrest, pulmonary edema and/or severe hypotension were seen in some critically ill patients with hypertrophic cardiomyopathy who were treated with verapamil.

Precautions: Verapamil should be given cautiously to patients with impaired hepatic function (in severe dysfunction use about 30% of the normal dose) or impaired renal function, and patients should be monitored for abnormal prolongation of the PR interval or other signs of overdosage. Verapamil may decrease neuromuscular transmission in patients with Duchenne's muscular dystrophy and may prolong recovery from the neuromuscular blocking agent vecuronium. It may be necessary to decrease verapamil dosage in patients with attenuated neuromuscular transmission. Combined therapy with beta-adrenergic blockers and verapamil may result in additive negative effects on heart rate, atrioventricular conduction and/or cardiac contractility; there have been reports of excessive bradycardia and AV block, including complete heart block. The risks of such combined therapy may outweigh the benefits. The combination should be used only with caution and close monitoring. Decreased metoprolol and propranolol clearance may occur when either drug is administered concomitantly with verapamil. A variable effect has been seen with combined use of atenolol. Chronic verapamil treatment can increase serum digoxin levels by 50% to 75% during the first week of therapy, which can result in digitalis toxicity. In patients with hepatic cirrhosis, verapamil may reduce total body clearance and extrarenal clearance of digitoxin. The digoxin dose should be reduced when verapamil is given, and the patient carefully monitored. Verapamil will usually have an additive effect in patients receiving blood-pressure-lowering agents. Disopyramide should not be given within 48 hours before or 24 hours after verapamil administration. Concomitant use of flecainide and verapamil may have additive effects on myocardial contractility, AV conduction, and repolarization. Combined verapamil and quinidine therapy in patients with hypertrophic cardiomyopathy should be avoided, since significant hypotension may result. Concomitant use of lithium and verapamil may result in an increased sensitivity to lithium (neurotoxicity), with either no change or an increase in serum lithium levels; however, it may also result in a lowering of serum lithium levels. Patients receiving both drugs must be monitored carefully. Verapamil may increase carbamazepine concentrations during combined use. Rifampin may reduce verapamil bioavailability. Phenobarbital may increase verapamil clearance. Verapamil may increase serum levels of cyclosporin. Verapamil may inhibit the clearance and increase the plasma levels of theophylline. Concomitant use of inhalation anesthetics and calcium antagonists needs careful titration to avoid excessive cardiovascular depression. Verapamil may potentiate the activity of neuromuscular blocking agents (curare-like and depolarizing), dosage reduction may be required. There was no evidence of a carcinogenic potential of verapamil administered to rats for 2 years. A study in rats did not suggest a tumorigenic potential, and verapamil was not mutagenic in the Ames test. Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy, labor, and delivery only if clearly needed. Verapamil is excreted in breast milk; therefore, nursing should be discontinued during verapamil use.

Adverse Reactions: Constipation (7.3%), dizziness (3.3%), nausea (2.7%), hypotension (2.5%), headache (2.2%), edema (1.9%), CHF, pulmonary edema (1.8%), fatigue (1.7%), dyspnea (1.4%), bradycardia: HR < 50/min (1.4%), AV block: total 1°,2°,3° (1.2%), 2° and 3° (0.8%), rash (1.2%), flushing (0.6%), elevated liver enzymes, reversible non-obstructive paralytic ileus. The following reactions, reported in 1.0% or less of patients, occurred under conditions where a causal relationship is uncertain: angina pectoris, atrioventricular dissociation, chest pain, claudication, myocardial infarction, palpitations, purpura (vasculitis), syncope, diarrhea, dry mouth, gastrointestinal distress, gingival hyperplasia, ecchymosis or bruising, cerebrovascular accident, confusion, equilibrium disorders, insomnia, muscle cramps, paresthesia, psychotic symptoms, shakiness, somnolence, arthralgia and rash, exanthema, hair loss, hyperkeratosis, macules, sweating, urticaria, Stevens-Johnson syndrome, erythema multiforme, blurred vision, gynecomastia, galactorrhea/hyperprolactinemia, increased urination, spotty menstruation, impotence.

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ARIZONA

The following list of continuing medical education programs in Arizona is compiled by the Arizona Medical Association. All courses listed have been certified as meeting the criteria for Category I of the ArMA CME Certificate and the AMA Physicians Recognition Award. To list Category I continuing medical education programs, please send information to Arizona Medical Association, 810 West Bethany Home Road, Phoenix, AZ 85013; or phone (602) 246-8901.

Brochures and registration forms are available from the contact person or organization sponsoring the program.

October 29-30—**Annual Southwestern Poison Symposium.** University of Arizona College of Medicine, Tucson. Fri-Sat. Contact: Lynn Mascarella, U of A.

October 29-30—**Hematology and Oncology for Primary Care Physicians.** Mayo Clinic, Scottsdale at the Orange Tree Golf and Conference Center, Scottsdale. Fri-Sat. Contact: Mayo Clinic-Scottsdale.

November 4-5—**Advanced Cardiac Life Support; Provider Course.** Maricopa Medical Center at MMC Conference Center, Phoenix. Thurs-Fri. Contact: (602) 267-5414.

November 5-6—**Parkinson's Disease and Movement Disorders for the Practitioner.** Mayo Clinic-Scottsdale at the Ritz Carlton Hotel, Phoenix. Fri-Sat. Contact: Mayo Clinic-Scottsdale.

November 11-13—**Sixth Annual Techniques in Gynecologic Surgery.** Mayo Clinic-Scottsdale at Marriott's Camelback Inn, Scottsdale. Thurs-Sat. Contact: Mayo Clinic-Scottsdale.

November 12-13—**Inflammatory Bowel Disease Conference.** Mayo Clinic-Scottsdale at Ashton B. Taylor Auditorium, Scottsdale. Fri-Sat. Contact: Mayo Clinic-Scottsdale.

November 13—**Vascular Symposium.** University of Arizona College of Medicine, Tucson. Sat. Contact: Lynn Mascarella, U of A.

November 16-17—**Pediatric Advanced Life Support; Provider Course.** Maricopa Medical Center at MMC Conference Center, Phoenix. Tues-Wed. Contact: (602) 267-5414.

November 18-21—**15th Annual Conference on Patient Education: Informing the Patient; Reforming the System.** American Academy of Family Physicians at Wyndam Paradise Valley Resort, Scottsdale. Thurs-Sun. Contact: Health Education Department, (800) 274-2237.

November 19—**Fifth Annual Update on Arthritis.** University of Arizona College of Medicine at Westin La Paloma Resort, Tucson. Fri. Contact: U of A.

November 19-20—**Molecular Biology: Applications in Clinical Medicine.** Mayo Clinic-Scottsdale at the Orange Tree Golf and Country Club, Scottsdale. Fri-Sat. Contact: Mayo Clinic-Scottsdale.

CONTACT INFORMATION

ArMA—Contact: Arizona Medical Association, 810 W. Bethany Home Rd, Phoenix, AZ 85013. (602) 246-8901.

Mayo Clinic-Scottsdale—Contact: Postgraduate Courses, Mayo Clinic-Scottsdale, (602) 301-7447.

U of A—Contact: University of Arizona College of Medicine, Arizona Health Sciences Center, Tucson, AZ 85724. (602) 626-7832.

CALIFORNIA, HAWAII, AND NEVADA

This listing of continuing education programs in California, Hawaii, and Nevada is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Karen Williams, Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690; or phone (415) 882-5183. For more information on accreditation or certification, please write to the above address.

ANESTHESIOLOGY

November 12-14—**Anesthesiology Update: 1993.** UCD at Monterey Plaza. Fri-Sun. 14 hrs. $275-$375. Contact: UCD.

November 19-20—**3rd Annual Pain Management.** UCD at Silverado Country Club, Napa. Fri-Sat. Contact: UCD.

January 16-22—**Hawaiian Seminar on Clinical Anesthesia.** California Society of Anesthesiologists at Westin Maui, Kaanapali Beach. Sun-Sat. 21 hrs. $425. Contact: CSA, 1065 E Hillsdale Blvd, Ste 410, Foster City 94404. (800) 345-3691.

January 28-30—**32nd Clinical Conference in Pediatric Anesthesiology.** Children's Hospital Los Angeles at Disneyland Hotel, Anaheim. Fri-Sun. 15 hrs. Contact: Children's Hospital, PO Box 54700, Los Angeles 90054. (213) 669-2262.

March 19-20—**Case Conference in Anesthesia.** California Society of Anesthesiologists at Dana Point Resort. Sat-Sun. 9 hrs. $185. Contact: CSA, 1065 E Hillsdale Blvd, Ste 410, Foster City 94404. (800) 345-3691.

April 9-10—**39th PGA Conference.** Los Angeles County Society of Anesthesiologists at UCLA Faculty Center. Sat-Sun. 13 hrs. Contact: LACSA, PO Box 90999, Long Beach 90809-0999. (213) 597-2661.

CARDIOLOGY

November 5-6—**Update in Electrocardiography and Arrhythmias.** UCSF at Pan Pacific Hotel, San Francisco. Fri-Sat. 8 hrs. $100. Contact: UCSF.

DERMATOLOGY

January 21-23—**Cutaneous Malignancies: 1994 Skin Cancer Update.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Fri-Sun. 17 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

January 21-23—**Practical Dermatology and Dermatologic Office Procedures for the Primary Care Physician.** UCSD at Hyatt Regency, La Jolla. Fri-Sun. 20 hrs. $495. Contact: Jacqueline Shiller, (619) 223-2997.

EMERGENCY MEDICINE

November 1-5—**22nd Annual Topics in Emergency Medicine.** UCSF at Miyako Hotel, San Francisco. Mon-Fri. 31 hrs. $575. Contact: UCSF.

November 5-6—**Medical Disaster Response Training Course.** American College of Emergency Physicians California Chapter at Doubletree Hotel and UCI Medical Center, Orange. Fri-Sat. 16 hrs. $350. Contact: Carl Schultz, MD, PO Box 578, Dana Point 92629. (714) 248-2952.

November 8-12—**Emergency Medicine Symposium III.** UCSD at San Diego Hilton. Mon-Fri. 32 hrs. $495. Contact: UCSD.

December 5-10—**14th Annual Conference: Current Concepts in Emergency Care.** American College of Emergency Physicians Washington Chapter at Maui Intercontinental Resort, Maui, Hawaii. Sun-Fri. 20 hrs. Contact: Kailani World Travel, 4192 Meridian Ave, Box 9751, Bellingham, WA 98227. (800) 544-9269 or (206) 671-1800.

January 10-14—**Emergency Medicine Symposia I.** UCSD at La Jolla Marriott. Mon-Fri. 32 hrs. $495. Contact: UCSD.

January 22-29—**Update: Controversies in Emergency and Primary Care.** UCSD at The Royal Waikoloan, Kohala Coast, Hawaii. 1 wk. Contact: Edith Bookstein, PO Box 2586, La Jolla 92038. (619) 454-3212.

February 26-March 5—**Cardiac Emergencies.** UCSD at Royal Lahaina Resort, Maui, Hawaii. 1 wk. 21 hrs. $450. Contact: Edith Bookstein, PO Box 2586, La Jolla 92038. (619) 454-3212.

FAMILY PRACTICE/PRIMARY CARE

October 30—**Selected Topics in Cardiology: A Course for Primary Care Physicians.** UCLA at Miramar Sheraton Hotel, Santa Monica. Sat. 5 hrs. $40. Contact: UCLA Extension.

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❒ 43rd Annual Obesity and Associated Conditions Symposium, Nov 5-7, 1993, Sahara Hotel, Las Vegas, NV.
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October 25-28, 1993
KONA, HAWAII

NOVEMBER, 1993
6th Annual Obstetrical Ultrasound (Hands-on)
November 5-7, 1993
ORANGE, CALIFORNIA

4th Annual Management of Diabetes
November 12-13, 1993
NEWPORT BEACH, CALIFORNIA

Ethics of Futile Care
November 13, 1993
LONG BEACH, CALIFORNIA

DECEMBER, 1993
Thoracoscopy for the Pulmonologist
December 3-4, 1993
LONG BEACH, CALIFORNIA

Incontinence/Upper Tract Disease for the Primary Care Physician
December 10-12, 1993
CHICAGO, ILLINOIS

1994

JANUARY, 1994
9th Annual Perinatal Symposium
January 12-16, 1994
BEAVER CREEK, COLORADO

Advanced Urogynecological Surgery
January 16-20, 1994
GRAND CAYMAN, WEST INDIES

FEBRUARY, 1994
Current Concepts in Cancer Imaging
February 11-12, 1994
NEWPORT BEACH, CALIFORNIA

The Neurologist and Back Pain
February 12-14, 1994
NEWPORT BEACH, CALIFORNIA

Incontinence/Upper Tract Disease for the Primary Care Physician
February 17-20, 1994
LOS ANGELES, CALIFORNIA

15th Annual Symposium Current Topics in Obstetrics
February 19-26, 1994
ASPEN, COLORADO

MARCH, 1994
Oncology for the Gynecologist
March 7-11, 1994
LAKE TAHOE, CALIFORNIA

Gynecologic Surgery
March 10-12, 1994
PALM SPRINGS, CALIFORNIA

19th Annual Care of the Sick Newborn
March 23-25, 1994
LONG BEACH, CALIFORNIA

APRIL, 1994
3rd Annual OB/GYN Ultrasound
April 5-8, 1994
MAUI, HAWAII

Sweet Success Meeting
April 20-22, 1994
IRVINE, CALIFORNIA

MAY, 1994
5th Annual Philip J. DiSaia Society Obstetric Gynecology Symposium
May 13, 1994
ORANGE, CALIFORNIA

JUNE, 1994
UCI Family Practice Refresher Course
June 13-18, 1994
NEWPORT BEACH, CALIFORNIA

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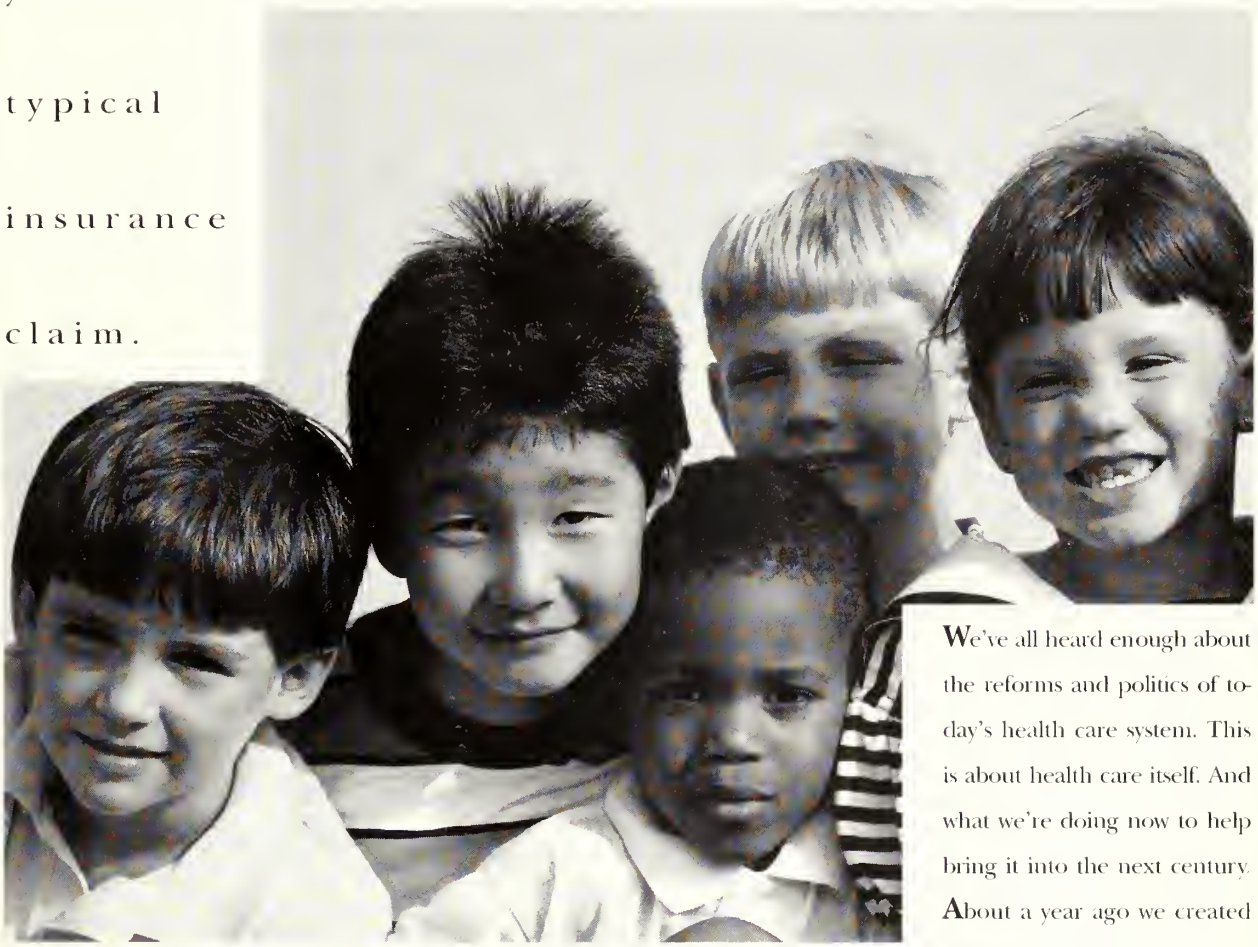

We've all heard enough about the reforms and politics of today's health care system. This is about health care itself. And what we're doing now to help bring it into the next century. About a year ago we created CaliforniaKids,℠ a statewide program that helps children without health coverage get free access to preventive and standard health care. In Pacoima, we're helping to establish a medical clinic at Vaughn Street Elementary School, where many of the children are in need of quality care. Medi-Cal beneficiaries in Sacramento County now have access to quality care through a new network which includes our Prudent Buyer℠ providers. And in Oakland, we helped create a pilot program for pre-pregnancy counseling to high-risk teens. It's only a start, to be sure. But these programs represent our commitment to better, more accessible health care for everyone. And that's not a claim. It's a promise.

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November 10-13—**North American Primary Care Research Group—Research Frontiers in Primary Care and Prevention.** UCSD at Hyatt Islandia on Mission Bay, San Diego. Wed-Sat. 23 hrs. $400. Contact: UCSD.

November 13—**Updated Neurology for the Primary Care Physician.** UCD at the Cancer Center Auditorium, Sacramento. Sat. 7 hrs. $95. Contact: UCD.

December 2-4—**Obstetrics and Gynecology Conference.** University of Nebraska at Bally's Las Vegas. Thurs-Sat. $275. Contact: University of Nebraska Medical Center, 600 S 42nd St, Omaha, NE 68198-5651. (402) 559-4152 or (800) 642-1095.

January 21-23—**Practical Dermatology and Dermatologic Office Procedures for the Primary Care Physician.** UCSD at Hyatt Regency, La Jolla. Fri-Sun. 20 hrs. $495. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

February 5-12—**5th Kaiser Permanente National Conference on Musculoskeletal Medicine.** Kaiser Permanente at Hyatt Regency, Kauai, Hawaii. 1 week. 29 hrs. $400. Contact: Ferdy Massimino, MD, 200 Muir Rd, Martinez 94553. (510) 372-1457.

February 18-20—**Office Gynecology for the Primary Care Physician.** SDSU at Hyatt Islandia, San Diego. Fri-Sun. 20 hrs. $450. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

March 23-25—**Annual Review in Family Medicine: Controversies and Challenges in Primary Care.** UCSF at Hotel Nikko, San Francisco. Wed-Fri. 16 hrs. $300. Contact: UCSF.

1993-1994—**HIV Primary Care Mini-Residency.** UCSD at Owen Clinic, San Diego. Ongoing. 30 hrs. Contact: UCSD.

GERIATRICS

November 8-10—**Geriatrics Update: 1993.** Sharp Memorial Hospital at Loew's Coronado Bay Resort, San Diego. Mon-Wed. 20 hrs. $425. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

January 18-22—**11th Annual Intensive Course in Geriatric Medicine and Board Review.** UCLA at Beverly Hilton Hotel, Beverly Hills. Tues-Sat. 44 hrs. $675. Contact: UCLA.

KEY TO ABBREVIATIONS

CMA California Medical Association
Contact: Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690. (415) 541-0900.

CPMC: California Pacific Medical Center
Contact: Continuing Education, California Pacific Medical Center, PO Box 7999, San Francisco 94120. (415) 923-3441.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Herbert M. Thomas, MD, MPH, Director of CME, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th St, Los Angeles 90059. (213) 603-3183.

LLU: Loma Linda University
Contact: James J. Couperus, MD, Associate Dean for Educational Affairs, Loma Linda University School of Medicine, Loma Linda 92350.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Medical School Office Building, Suite X-365, Stanford 94305-6114. (415) 723-5594.

UCD: University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, 2701 Stockton Blvd, Sacramento 95817. (916) 734-5390.

UCI: University of California, Irvine
Contact: Melvin I. Marks, MD, Director, Memorial/UCI Center for Health Education, Long Beach Memorial Medical Center, 2801 Atlantic Ave, PO Box 1428, Long Beach, California 90801-1428. (213) 595-3811.

UCLA: University of California, Los Angeles Extension
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, PO Box 24902, UCLA, Los Angeles 90024. (310) 825-8423.

UCSD: University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (619) 534-3940.

UCSF: University of California, San Francisco
Contact: Janet Johnson, Administrative Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 476-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 1975 Zonal Ave, KAM314, Los Angeles 90033. (800) 872-1119.

1993-1994—**Mini-residency in Geriatrics.** UCSD at Multi Purpose Facility, San Diego. Ongoing. 40-80 hrs. $195. Contact: UCSD.

1993-1994—**The GGG/Alzheimer's Family Center: Sharing the Caring—Training Series on Dementia.** UCSD. Ongoing. 4 hrs. $25. Contact: UCSD.

INFECTIOUS DISEASES

November 5-7—**Advances in Infectious Disease.** Sharp Memorial Hospital at Loew's Coronado Bay Resort, San Diego. Fri-Sun. 20 hrs. $425. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

November 6—**New Developments in Infectious Disease.** UCSF at Quail Lodge, Carmel. Sat. Contact: UCSF.

December 13-15—**Clinical Care of the AIDS Patient.** UCSF at Sheraton Palace Hotel, San Francisco. Tues-Thurs. 15 hrs. $295. Contact: UCSF.

INTERNAL MEDICINE

February 3-5—**17th Annual Neurology for the Non-Neurologists.** UCSD at Pan Pacific Hotel, San Diego. Thurs-Sat. 21 hrs. $450. Contact: Edith Bookstein, PO Box 2586, La Jolla 92038. (619) 454-3212.

February 5—**New Advances in Inflammatory Bowel Disease.** Scripps Clinic and Research Foundation at Green Hospital Amphitheater. Sat. 7 hrs. $140. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

February 26-27—**Endoscopy 1994.** Southern California Society for Gastrointestinal Endoscopy at Century Plaza Hotel, Los Angeles. Sat-Sun. Contact: Joyce M. Fried, 10833 Le Conte Ave, Los Angeles 90024-1722. (310) 374-9708.

March 18-24—**Internal Medicine: 1994.** Sharp Memorial Hospital at Hotel del Coronado, San Diego. Fri-Thurs. 54 hrs. $695. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

OB/GYN

November 20—**Infertility Update VII.** Scripps Clinic and Research Foundation, La Jolla. Sat. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

December 2-3—**Controversies in Women's Health.** UCSF at Hotel Nikko, San Francisco. Thurs-Fri. Contact: UCSF.

December 2-4—**Obstetrics and Gynecology Conference.** University of Nebraska at Bally's Las Vegas. Thurs-Sat. $275. Contact: University of Nebraska Medical Center, 600 S 42nd St, Omaha, NE 68198-5651. (402) 559-4152 or (800) 642-1095.

OCCUPATIONAL/ENVIRONMENTAL

January 31-February 4—**Occupational and Environmental Medicine.** UCSF at Miyako Hotel, San Francisco. Mon-Fri. Contact: UCSF.

ONCOLOGY

October 25-27—**17th Annual Cancer Symposium.** Scripps Memorial Hospital at Sheraton Harbor Island Hotel, San Diego. Mon-Wed. 20 hrs. $390. Contact: Cancer Symposium Conference Office, PO Box 16502, Irvine 92713-6338. (800) 321-6338.

October 30-31—**12th Annual Cancer Memorial Symposium: Palliative Care for Metastatic Disease.** Hi Desert Joint Cancer Program at Holiday Inn Victorville. Sat-Sun. 9 hrs. $90. Contact: Alice Williams, 15248 11th St, Victorville 92392. (619) 245-8691, ext. 3432.

November 4-5—**Growth Control, Signal Transduction and Oncogenesis.** UCLA at Beverly Hilton Hotel, Beverly Hills. Thurs-Sat. 12.75 hrs. $113-$150. Contact: UCLA Extension.

November 5-6—**American College of Surgeons: Cancer Management Course.** UCD at Cancer Center Auditorium, Sacramento. Fri-Sat. 13 hrs. $400. Contact: UCD.

November 20—**Breast Cancer: New Directions.** UCSF at Sheraton Palace Hotel, San Francisco. Sat. Contact: UCSF.

December 5—**Tumors of the Female Genital Tract.** California Tumor Tissue Registry at Ritz-Carlton Hotel, San Francisco. Sat. 8 hrs. $55. Contact: California Tumor Tissue Registry, c/o Loma Linda University, 11021 Campus Ave, AH 335, Loma Linda 92354. (909) 824-4788.

February 21-23—**Clinical Hematology and Oncology: 1994.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Mon-Wed. 18 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

(Continued on Page 441)

CONTINUING MEDICAL EDUCATION

(Continued from Page 440)

OPHTHALMOLOGY

December 9-11—**Cornea and Excimer Update Symposium and Workshop.** UCSF at Ana Hotel and University, San Francisco. Thurs-Sat. 13 hrs. Contact: UCSF.

ORTHOPEDICS

October 29-30—**Revision Total Hip in the 1990s.** American Academy of Orthopedic Surgeons at US Grant Hotel, San Diego. Fri-Sat. Contact: AAOS, 6300 N River Rd, Rosemont, IL 60018-4262. (800) 346-2207.

November 5-9—**Fractures of the Pelvis and Acetabulum.** American Academy of Orthopedic Surgeons at Marriott's Rancho Las Palmas Resort and Country Club Annenberg Center, Eisenhower Medical Center, Rancho Mirage. Fri-Tues. Contact: AAOS, 6300 N River Rd, Rosemont, IL 60018-4262. (800) 346-2207.

December 1-4—**Cost Effective Back Care.** American Back Society at San Francisco Hilton & Towers. Wed-Sat. Contact: Aubrey Swartz, 2647 E 14th St, Ste 401, Oakland 94601. (510) 536-9929.

December 3-5—**Review and Update for Practicing Orthopedic Surgeons.** American Academy of Orthopedic Surgeons at Sheraton Palace Hotel, San Francisco. Fri-Sun. Contact: AAOS, 6300 N River Rd, Rosemont, IL 60018-4262. (800) 346-2207.

December 8-12—**American Back Society Meeting.** American Back Society at Hyatt Regency Embarcadero, San Francisco. Wed-Sun. Contact: ABS, 2647 E 14th St, Ste 401, Oakland 94601. (510) 536-9929.

January 20-23—**Reconstruction of the Adult Hip: A Comprehensive Course.** American Academy of Orthopedic Surgeons at Hyatt Regency Maui, Lahaina, Hawaii. Thurs-Sun. Contact: AAOS, 6300 N River Rd, Rosemont, IL 60018-4262. (708) 823-7186.

January 27-30—**Spring Meeting of the Northern California Chapter of the Western Orthopedic Association** at Inn at Squaw Creek, Olympic Valley. Thurs-Sun. Contact: Iola Beckley, (707) 538-5548.

(Continued on Page 444)

2nd Ambulatory Health Care Accreditation Conference

The California Medical Association's Ambulatory Care Review Committee and the Accreditation Association for Ambulatory Health Care, Inc. present the second *Ambulatory Health Care Accreditation Conference* on December 3, 1993, at the Los Angeles Airport Hilton Hotel. All aspects of the CMA-AAAHC Ambulatory Review Program will be addressed. This program is approved for two hours of Category I credit.

FOR FURTHER INFORMATION and registration please direct all inquiries to: Anne Ahrens, California Medical Association, P.O. Box 7690, San Francisco, CA 94120-7690, 415/882-5174.

American Academy of Cosmetic Surgery

10th Annual Scientific Meeting

The outstanding educational session lineup—developed by Douglas D. Dedo, MD, program chair—will include early bird workshops featuring glycoric acid skin care; facial plastic surgery; liposuction surgery; and hair restoration surgery.

Free Paper presentation topics include:

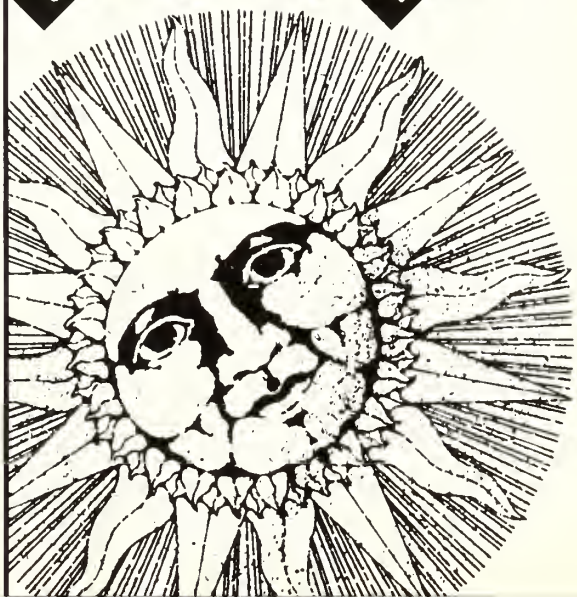
- Facial and general body plastic surgery
- Lipo Sculpture
- New technologies in laser surgery and endoscopy
- Hair restoration...Plus a special extended workshop on hair restoration featuring anatomy dissection will be offered during the meeting.

The meeting's keynote speaker is noted transsexual surgery specialist Stanley H. Biber, MD. For registration or exhibiting information please contact...

AMERICAN ACADEMY OF COSMETIC SURGERY

401 N. Michigan Avenue
Chicago, IL 60611-4267
312.527.6713
FAX: 312.644.1815

Celebrating a Decade of Progress
January 21-23, 1994
Westin Mission Hills Resort
Rancho Mirage, California



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506 **Complications of Do-Not-Resuscitate Orders**
JONATHAN HARDING, MD
PHILIP S. MEHLER, MD
STEVEN R. LOWENSTEIN, MD, MPH, Responds

507 **The Potential Effects of Enterprise Liability**
SANFORD E. FELDMAN, MD

508 **Cocaine Toxicity in Glycogen Storage Disease**
BRUCE E. WILSON, MD, and WILLIAM N. HOBBS, MD

509 **Advances in Cutaneous Laser Surgery**
RICHARD E. FITZPATRICK, MD, and MICHAEL P. GOLDMAN, MD
THOMAS R. STEVENSON, MD, Responds

510 **Audible Third Heart Sound**
DAVID A. NARDONE, MD
PAUL A. SOBOTKA, MD, and DAVID L. BUSHNELL, MD, Respond

511 **Improving Drug Therapy in the Elderly**
R. RON FINLEY, BSPharm, and ANDREW L. LEEDS, PharmD

512 **Why Physicians Retire Continued**
ALEX MILYKO, MD

512 **Access to Obstetric Care—The San Diego Experience**
VAL CATANZARITE, MD, PhD, and LINDA WHITE, MSW, LCSW
BARBARA M. AVED, PhD; MARY M. IRWIN; LESLEY S. CUMMINGS, MPA; and NANCY FINDEISEN Respond

LESSONS FROM THE PRACTICE

514 **The Wake-up Call**
JOYCE ADAMS, MD
From the Fresno-Central San Joaquin Valley Medical Education Program, University of California, San Francisco, School of Medicine, and the Department of Pediatrics, Valley Medical Center, Fresno, California.

OTHER FEATURES

436 **Continuing Medical Education Activities in Arizona; California, Hawaii, and Nevada; Colorado; New Mexico; Utah; Washington; Wyoming**

454 **Poem**

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518 **In Memoriam**

520 **Classified Advertising**

529 **Western State Medical Associations' Meetings**

★ Official Journal of the Alaska State Medical Association, the Arizona Medical Association, the California Medical Association, the Denver Medical Society, the Idaho Medical Association, the Nevada State Medical Association, the New Mexico Medical Society, the Utah Medical Association, the Washington State Medical Association, and the Wyoming Medical Society.

★ Affiliated Clinical Investigation Societies: the Western Association of Physicians; the Western Society for Clinical Investigation; the Western Section, American Federation for Clinical Research; the Western Society for Pediatric Research; the Western Region, Society for Investigative Dermatology.

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We become part of your office staff

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(Continued from Page 441)

OTOLARYNGOLOGY

November 4-6—**The San Francisco Otology, Neurotology, and Skull Base Surgery Update—1993.** UCSF at Ritz-Carlton Hotel, San Francisco. Thurs-Sat. 22 hrs. $395. Contact: UCSF.

November 14-19—**Temporal Bone Dissection Course.** House Ear Institute. Sun-Fri. 53 hrs. $875-$1,100. Contact: Antonio De la Cruz, 2100 W Third St, Los Angeles 90057. (213) 483-4431 ext. 7079.

PATHOLOGY

October 25-29—**19th Annual Lukes Conference: Diagnostic Approaches to Lymphoproliferative Disorders.** Fri-Tues. 27 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

PEDIATRICS

December 4-5—**Stabilization and Management of the Critically Ill Child.** UCSF at San Francisco. Sat-Sun. 9 hrs. $220. Contact: UCSF.

January 24-28—**San Diego Conference on Responding to Child Maltreatment.** Children's Hospital San Diego at Town and Country Hotel, San Diego. Mon-Fri. $390. Contact: Center for Child Protection, 8001 Frost St, San Diego 92123. (619) 395-4950.

February 21-23—**Pediatrics Update 1994.** San Diego State University at Hyatt Islandia, San Diego. Mon-Wed. 20 hrs. $450. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2297.

PSYCHIATRY

October 5-November 16—**Hypnotherapy with Sexually Abused Patients: Treatment Strategies, Techniques and Ethical Issues.** UCLA at Westwood United Methodist Church. Tuesdays. 14 hrs. $160. Contact: UCLA Extension.

November 12-14—**Group Therapy Symposium.** UCSF at Union Square Holiday Inn, San Francisco. Fri-Sun. 21 hrs. $235. Contact: UCSF.

November 18-20—**Addiction Medicine: State of the Art 1993.** California Society of Addiction Medicine at Four Seasons Hotel, Newport Beach. Thurs-Sat. 19 hrs. $350. Contact: CSAM, 3803 Broadway, Oakland 94611. (510) 428-9091.

January 23-28—**20th Annual Midwinter Program in Continuing Medical Education for Psychiatrists.** UCD at Hyatt Regency Lake Tahoe, Incline Village, Nevada. Sun-Fri. 25 hrs. $395. Contact: UCD.

February 26—**1994 Sleep Medicine Update.** Scripps Clinic and Research Foundation at La Jolla. Sat. 7 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

RADIOLOGY

October 25-29—**18th Annual San Diego Postgraduate Radiology Course.** UCSD at Hotel del Coronado, San Diego. Mon-Fri. 25 hrs. $595. Contact: UCSD.

October 29-31—**Annual Interventional Radiology Course.** UCSD at Hotel del Coronado, San Diego. Fri-Sun. 16 hrs. $375. Contact: UCSD.

November 12-14—**Advanced Seminars in Diagnostic Imaging.** UCSD at Ritz-Carlton, Laguna Niguel. Fri-Sun. 20 hrs. $500. Contact: UCSD.

January 17-19—**Neuroradiology Update.** Stanford University Medical Center at Ritz-Carlton, Laguna Niguel. Mon-Wed. 17.5 hrs. $450. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

January 20-23—**Breast Imaging Update.** Stanford University Medical Center at Ritz-Carlton Hotel, Laguna Niguel. Thurs-Sun. 16 hrs. $450. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

February 14-18—**Contemporary Diagnostic Imaging.** Stanford University Medical Center at Ritz-Carlton Resort Hotel, Kapalua, Hawaii. Mon-Fri. 20.5 hrs. $550. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925.

February 14-18—**Magnetic Resonance Imaging.** UCSD at Hotel del Coronado, San Diego. Mon-Fri. 30 hrs. $425. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

March 7-10—**Magnetic Resonance Imaging.** UCSD at Hotel del Coronado, San Diego. Mon-Thurs. 30 hrs. $625. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

March 21-26—**Musculoskeletal and Neuro MRI.** UCSD at La Costa Resort and Health Spa, Carlsbad. Mon-Sat. 19.5 hrs. $550. Contact: UCSD.

1993-1994—**Fellowship in Interventional Radiology for Radiologists.** UCSD Medical Center. Ongoing. 40 hrs. $700. Contact: UCSD.

1993-1994—**Visiting Fellowship in Magnetic Resonance Imaging.** UCSD at MR Institute, San Diego. Ongoing. 40 hrs. $1,200. Contact: UCSD.

1993-1994—**Visiting Fellowship for Physicians and Sonographers in Duplex Ultrasound: Focus on Carotid and Deep Venous Thrombosis.** Ongoing. 30 hrs. $600. Contact: UCSD.

GENERAL/MULTIDISCIPLINARY

October 27-31—**CME/Golf Meeting.** Nevada Academy of Family Physicians Las Vegas Chapter at Rio Hotel, Las Vegas. Wed-Sun. 23 hrs. $75. Contact: Barbara Bolling, PO Box 27713, Las Vegas, NV 89126-1713. (702) 647-0117.

October 30—**Low Back Pain and Workers' Compensation.** Sutter Community Hospitals, Sacramento. Sat. Contact: Lynne MacRae, 2800 L St, Sacramento 95816. (916) 733-3883.

January 7-9—**7th Annual Medical Office Laboratory Conference.** SDSU at Red Lion Hotel, San Diego. Fri-Sun. 20 hrs. $425. Contact: Nancy Geiser, (619) 594-6255.

February 12-13—**Clinical Applications of Vestibular Science.** UCLA. Sat-Sun. $350. Contact: Marjorie Harris, 15-50 Rehabilitation Center, UCLA 90024. (310) 825-5131.

HOME STUDY/SELF ASSESSMENT

Audio-Digest Foundation. California Medical Association. Contact: Audio-Digest Foundation, 1577 E Chevy Chase, Glendale 91206. (213) 245-8505.

COLORADO

This listing of continuing medical education programs in Colorado is compiled by the Denver Medical Society. To list CME programs here, please send information at least two months in advance to: Mr Robert L. Kennedy, Denver Medical Society, 1850 Williams Street, Denver, CO 80218; or telephone (303) 377-1850.

Brochures, course information, and registration forms are available from the contact person or organization.

November 5-6—**16th Annual Perinatal Conference.** Children's Hospital of Denver at Laramie, Wyoming. Fri-Sat. Contact: Conference Office, (303) 861-6946 or (800) 225-0010.

November 11-13—**Rural Perinatal Traineeship Program.** Children's Hospital, Denver. Thurs-Sat. Contact: Outreach Office, (303) 861-6668.

December 18—**Computers in Medicine.** Rose Medical Center at Hotel L'Ostello, Vail. Sat. Repeated weekly through April 23, 1994, at either Hotel L'Ostello, Vail, or Hotel Wildwood, Snowmass Village. Contact: Bernard Karshmer, (800) 525-5810.

January 27-29—**Contemporary Management of Unstable Coronary Syndromes.** Department of Veterans Affairs at Beaver Run Resort, Breckenridge. Thurs-Sat. Contact: Karen Babcock, (303) 393-2826.

January 29-February 5—**Internal Medicine Conference.** Rose Medical Center at Radisson Resort, Vail. Sat-Sat. Contact: Bernard Karshmer, (800) 525-5810.

February 5-12—**General Surgery Conference.** Rose Medical Center at Radisson Resort, Vail. Sat-Sat. Contact: Bernard Karshmer, (800) 525-5810.

February 12-19—**Emergency Medicine Conference.** Rose Medical Center at Radisson Resort, Vail. Sat-Sat. Contact: Bernard Karshmer, (800) 525-5810.

February 12-19—**Psychiatry Conference.** Rose Medical Center at Radisson Resort, Vail. Sat-Sat. Contact: Bernard Karshmer, (800) 525-5810.

February 19-26—**Neurology Conference.** Rose Medical Center at the Antlers Hotel, Vail. Sat-Sat. Contact: Bernard Karshmer, (800) 525-5810.

February 19-26—**Obstetrics and Gynecology Conference.** Rose Medical Center at Radisson Resort, Vail. Sat-Sat. Contact: Bernard Karshmer, (800) 525-5810.

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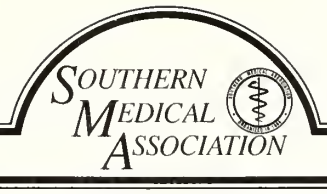


CONTINUING MEDICAL EDUCATION CALENDAR

The Southern Medical Association is accredited by the Accreditation Council for Continuing Medical Education to sponsor continuing medical education for physicians.

OCTOBER 28-31, 1993

SOUTHERN
MEDICAL
ASSOCIATION'S
87TH ANNUAL SCIENTIFIC ASSEMBLY
LOCATION: New Orleans Convention Center, New Orleans, Louisiana
FEATURES:
- 25 Medical Specialty Section Meetings
- 19 Joint Specialty Section Meetings
- 34 Postgraduate Courses
- 15 Clinical and Scientific Symposia
- 29 Round Table Luncheon Sessions With Featured Experts

and more...

CME CREDIT: AMA Category I, up to 25 Hours
FEE: SMA Member-$75; Nonmember-$200.
Fee waived for Physicians-in-Training

DECEMBER 3-4, 1993

SPA PSYCHIATRIC UPDATE
LOCATION: Birmingham, Alabama
SPECIALTY: Psychiatry
CME CREDIT: AMA Category I
FEE: SMA/SPA Member-$100; Nonmember-$200; Nonphysician-$50

DECEMBER 3-5, 1993

BURN SEMINAR
LOCATION: Orlando, Florida
SPECIALTY: Burn Center Directors and Health Care Professionals
CME CREDIT: AMA Category I
FEE: All Participants $75

JANUARY 28-30, 1994

KNEE SYMPOSIUM
LOCATION: Orlando, Florida
SPECIALTY: Orthopaedics
CME CREDIT: AMA Category I
FEE: SMA Member-$150; Nonmember-$300; Residents/Fellows-$50

JANUARY 29-FEBRUARY 5, 1994

PREVENTIVE MEDICINE
LOCATION: Tucson, Arizona
SPECIALTY: Primary Care
CME CREDIT: AMA Category I
FEE: SMA Member-$475; Nonmember-$600; Nonphysician-$300

FEBRUARY 2-4, 1994

ENT UPDATE
LOCATION: St. Thomas, Virgin Islands
SPECIALTY: Otolaryngology
CME CREDIT: AMA Category I
FEE: SMA Member-$475; Nonmember-$600; Nonphysician-$300

FEBRUARY 11-13, 1994

THE ATHLETIC PATIENT
LOCATION: Fort Lauderdale, Florida
SPECIALTY: Primary Care, Orthopaedics, Internal Medicine
CME CREDIT: AMA Category I–14 hours
FEE: SMA Member-$375; Nonmember-$500; Nonphysician-$250

For more information, call Michelle Williamson, Southern Medical Association, 800-423-4992 or 205-945-1840—TODAY!

(Continued from Page 444)

February 26-March 5—**Pediatrics Conference.** Rose Medical Center at Radisson Resort, Vail. Sat-Sat. Contact: Bernard Karshmer, (800) 525-5810.

February 26-March 5—**Infectious Disease Conference.** Rose Medical Center at the Antlers Hotel, Vail. Sat-Sat. Contact: Bernard Karshmer, (800) 525-5810.

March 5-12—**Primary Care Conference.** Rose Medical Center at Radisson Resort, Vail. Sat-Sat. Contact: Bernard Karshmer, (800) 525-5810.

March 5-12—**Minding the Body/Mending the Mind.** Rose Medical Center at the Antlers Hotel, Vail. Sat-Sat. Contact: Bernard Karshmer, (800) 525-5810.

March 6-11—**14th Annual Keystone ENT Conference.** University of Nebraska Medical Center at Keystone Resort, Keystone. Sun-Fri. Contact: U of Nebraska Continuing Education Center, (402) 559-4152.

March 12-19—**Sports Medicine Conference.** Rose Medical Center at Radisson Resort, Vail. Sat-Sat. Contact: Bernard Karshmer, (800) 525-5810.

March 12-19—**Urology Conference.** Rose Medical Center at Radisson Resort, Vail. Sat-Sat. Contact: Bernard Karshmer, (800) 525-5810.

March 19-26—**Cancer Treatment Conference.** Rose Medical Center at the Antlers Hotel, Vail. Sat-Sat. Contact: Bernard Karshmer, (800) 525-5810.

Tuesday Noon Conferences—**Various Topics in Medicine.** Lutheran Medical Center, Wheat Ridge. Contact: Jean A. Kline, (303) 425-2951.

Every Second Wednesday of the Month—**Cardiovascular Education Series.** St Anthony Hospitals at St Anthony Hospital, Denver. Contact: Rose Powell, (303) 629-3678.

Every Friday (except 4th Friday of month)—**Various Topics in Contemporary Medicine (Midday CME Series).** St Anthony Hospitals at St Anthony Hospital, Denver. Contact: Rose Powell, (303) 629-3678.

First Wednesday of Each Month—**Various Topics in Neurology.** Sponsored by the Colorado Society of Clinical Neurologists. Contact: Colorado Society of Neurologists, (303) 449-3566.

CONTACT INFORMATION

U of Colo—Contact: University of Colorado School of Medicine, Office of Continuing Medical Education, 4200 E 9th Ave, Denver, CO. (303) 270-5195 or (800) 882-9153; FAX (303) 270-6761.

NEW MEXICO

Information, requests for accreditation, and items to be listed should be sent to the chair of the CME Committee, New Mexico Medical Society, 7770 Jefferson, Suite 400, Albuquerque, NM 87109, at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 828-0237.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

November 11-14—**Violence Education Conference. Theme: Teaching About Violence: Curricula, Values, Obstacles, and Solutions.** Sheraton Old Town Inn, Albuquerque. Thurs-Sun. Contact: Program Department, Society of Teachers of Family Medicine, PO Box 8729, Kansas City, MO 64114. (800) 274-2237.

CONTACT INFORMATION

UNM SOM—University of New Mexico School of Medicine, Office of CME, PO Box 713, Albuquerque 87131. (505) 277-3942.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. Accredited institutions wishing to list AMA Category 1 CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, UT 84102; or phone (801) 355-7477. For information on CME accreditation, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution.

December 5-9—**Intensive Neuroradiology.** Marriott Hotel, Salt Lake City. Sun-Thurs. Contact: UUSM.

February 7-11—**Surgical Pathology.** Yarrow Hotel, Park City. Mon-Fri. Contact: UUSM.

February 14-18—**Update in Clinical Microbiology and Immunology.** Yarrow Hotel, Park City. Mon-Fri. Contact: UUSM.

February 17-24—**37th Anesthesiology Update: Anesthesia and the Nervous System.** Snowbird Cliff Lodge. 1 week. Contact: UUSM.

February 23-27—**Physical Medicine and Rehabilitation Update.** Prospector Square Conference Center, Park City. Wed-Sun. Contact: UUSM.

February 27-March 2—**35th Annual OB/GYN Update.** Yarrow Hotel, Park City. Sun-Wed. Contact: UUSM.

March 2-5—**Surgical Oncology Update.** Yarrow Hotel, Park City. Wed-Sat. Contact: UUSM.

March 6-11—**Advances in Internal Medicine.** Cottonwood Center, Snowbird. Sun-Fri. Contact: UUSM.

March 8-12—**Microsurgery Workshop.** University Park Hotel, Salt Lake City. Thurs-Sat. Contact: UUSM.

March 11-12—**Western Intermountain Neurological.** University Park Hotel, Salt Lake City. Fri-Sat. Contact: UUSM.

MEDICAL GRAND ROUNDS

Weekly—Internal Medicine Grand Rounds, Psychiatry Grand Rounds, OB/GYN Grand Rounds, Pediatric Grand Rounds. Contact: UUSM, Office of CME, (801) 581-8664.

SPONSORS OF COURSES—ABBREVIATIONS

CH: Castleview Hospital, 300 N Hospital Dr, Price 84501. (801) 637-4800.

CS: Charter Summit Hospital, 175 W 7200 South, Midvale 84047. (801) 561-8181.

DM: Dixie Medical Center, 544 S 400 East, St George 84770. (801) 634-4000.

ETS: Emergency Training Services, 777 N 390 East, American Fork 84003. (801) 763-3555.

FHP: FHP of Utah, 35 W Broadway, Salt Lake City 84101. (801) 355-1234

ITS: Intermountain Thoracic Society, 1616 S 11th East, Salt Lake City 84105. (801) 484-4456.

LDSH: LDS Hospital, 8th Ave and "C" St, Salt Lake City 84143. (801) 321-1100.

LRH: Logan Regional Hospital, 1400 N 5th East, Logan 84321. (801) 752-2050.

MVH: Mountain View Hospital, 1000 E Highway 6, Payson 84651. (801) 465-9201.

OSS: Ogden Surgical-Medical Society, PO Box 9311, Ogden 84409.

PCMC: Primary Children's Medical Center, 100 N Medical Dr, Salt Lake City 84113. (801) 588-2000.

PVH: Pioneer Valley Hospital, 3460 S 4155 West, West Valley City 84120. (801) 968-9061.

UMIA: Utah Medical Insurance Association, 540 E 500 South, Salt Lake City 84102. (801) 531-0375.

UMA: Utah Medical Association, 540 E Fifth South, Salt Lake City 84102. (801) 355-7477.

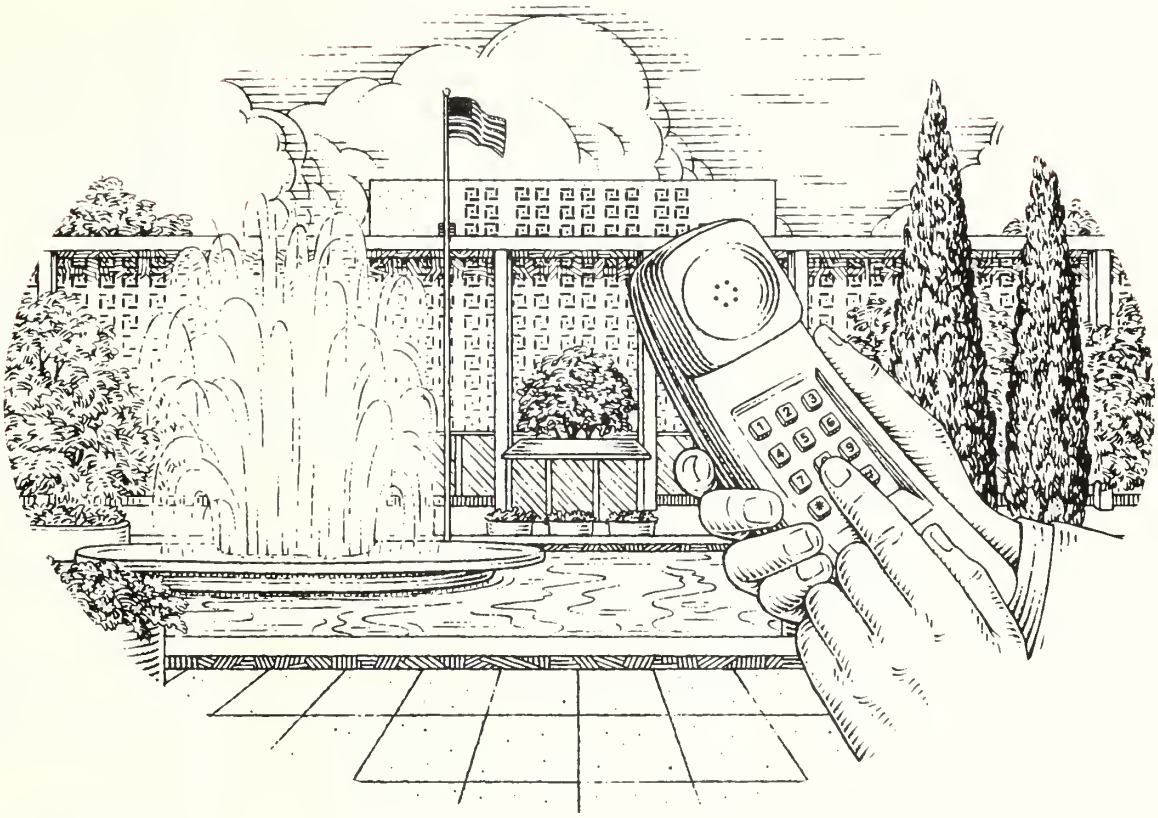
UOS: Utah Ophthalmological Society, 540 E 500 South, Salt Lake City 84102. (801) 355-7477.

USH: Utah State Hospital, PO Box 270, Provo 84603-0270. (801) 373-4400.

UUSM: University of Utah School of Medicine, Office of Continuing Medical Education, 50 N Medical Dr, Salt Lake City 84132. (801) 581-8664.

VAMC: Veterans Administration Medical Center, 500 Foothill Dr, Salt Lake City 84148. (801) 582-1565.

(Continued on Page 448)



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CONTINUING MEDICAL EDUCATION

(Continued from Page 446)

WASHINGTON

The listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here, please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 1100, Seattle, WA 98121; or phone (206) 441-9762 or (800) 552-0612.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

October 27—**Perinatology Conference.** Tacoma. Wed. Contact: Multicare, (206) 552-1221.

November 4-5—**Drug Therapy.** Seattle. Thurs-Fri. Contact: U/W.

November 10—**Infectious Disease.** Wed. Contact: Northwest Hospital, (206) 368-1623.

November 18-19—**Diabetes Update.** Thurs-Fri. Contact: U/W.

November 19—**Advances in Therapeutics for the Clinician.** Renton. Fri. Contact: VMC, (206) 228-3440.

December 2-4—**American College of Physicians.** Seattle. Thurs-Sat. Contact: U/W.

December 9-12—**9th Infectious Disease Conference.** Everett. Tues-Sat. Contact: PNMEII, (206) 258-6322.

December 10-11—**Mental Health Update.** Fri-Sat. Contact: U/W.

December 10-11—**Regional Musculoskeletal Conference.** Seattle. Fri-Sat. Contact: U/W.

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104. (206) 223-5953.

PCMS CME—Contact: Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 223-6898.

WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Suite 1100, Seattle, WA 98121. (206) 441-9762.

WYOMING

October 29-30—**16th Annual Perinatal Conference**, Children's Hospital of Denver at Laramie. Fri-Sat. Contact: Conference Office, (303) 861-6946 or (800) 225-0010. ◆

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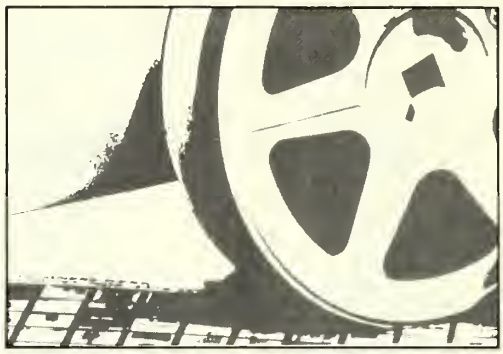

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FREE HIV RISK ASSESSMENT PROGRAM AVAILABLE

CMA's Department of Physician Education has produced a new CME program, "HIV Risk Assessment: Methods and Guidelines," which is available free to physicians. This program teaches effective strategies developed by expert physicians to identify patients who are potentially at risk for HIV infection. Worth one hour of CME Category I credit, the program is designed for groups of 5-20 physicians.

The program features CMA's award-winning, 11-minute video, "Let's Talk," which highlights several methods physicians can use to perform HIV assessment with patients. Participants receive a course outline, camera-ready slide reproductions, a compilation of state laws pertaining to HIV/AIDS, community resource guide to HIV testing and counseling, risk assessment guidelines, and a model HIV consent form and patient information pamphlet.

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Indications and Usage: *Augmentin* is indicated in the treatment of infections caused by susceptible strains of the designated organisms in the conditions listed below

Lower Respiratory Tract Infections caused by β-lactamase-producing strains of *Hemophilus influenzae* and *Moraxella (Branhamella) catarrhalis*

Otitis Media caused by β-lactamase-producing strains of *Hemophilus influenzae* and *Moraxella (Branhamella) catarrhalis*

Sinusitis caused by β-lactamase-producing strains of *Hemophilus influenzae* and *Moraxella (Branhamella) catarrhalis*

Skin and Skin Structure Infections caused by β-lactamase-producing strains of *Staphylococcus aureus, E. coli*, and *Klebsiella* spp

Urinary Tract Infections caused by β-lactamase-producing strains of *E. coli, Klebsiella* spp and *Enterobacter* spp

While *Augmentin* is indicated only for the conditions listed above, infections caused by ampicillin-susceptible organisms are also amenable to *Augmentin* treatment due to its amoxicillin content. Therefore, mixed infections caused by ampicillin-susceptible organisms and β-lactamase producing organisms susceptible to *Augmentin* should not require the addition of another antibiotic

Bacteriological studies, to determine the causative organisms and their susceptibility to *Augmentin*, should be performed together with any indicated surgical procedures

Therapy may be instituted prior to obtaining the results from bacteriological and susceptibility studies to determine the causative organisms and their susceptibility to *Augmentin* when there is reason to believe the infection may involve any of the β-lactamase-producing organisms listed above. Once the results are known, therapy should be adjusted, if appropriate

Contraindications: A history of allergic reactions to any penicillin is a contraindication

WARNINGS: SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTOID) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY. ALTHOUGH ANAPHYLAXIS IS MORE FREQUENT FOLLOWING PARENTERAL THERAPY, IT HAS OCCURRED IN PATIENTS ON ORAL PENICILLINS. THESE REACTIONS ARE MORE LIKELY TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR A HISTORY OF SENSITIVITY TO MULTIPLE ALLERGENS. THERE HAVE BEEN REPORTS OF INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS. BEFORE INITIATING THERAPY WITH ANY PENICILLIN, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS OR OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, *AUGMENTIN* SHOULD BE DISCONTINUED AND THE APPROPRIATE THERAPY INSTITUTED. **SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE, OXYGEN, INTRAVENOUS STEROIDS AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.**

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including *Augmentin*, and has ranged in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is 1 primary cause of "antibiotic associated colitis."

Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation and treatment with an antibacterial drug clinically effective against *C. difficile* colitis

Precautions: General: While *Augmentin* possesses the characteristic low toxicity of the penicillin group of antibiotics, periodic assessment of organ system functions, including renal, hepatic and hematopoietic function, is advisable during prolonged therapy

A high percentage of patients with mononucleosis who received ampicillin develop a skin rash. Thus, ampicillin class antibiotics should not be administered to patients with mononucleosis

The possibility of superinfections with mycotic or bacterial pathogens should be kept in mind during therapy. If superinfections occur (usually involving *Pseudomonas* or *Candida*), the drug should be discontinued and/or appropriate therapy instituted

Drug Interactions: Probenecid decreases the renal tubular secretion of amoxicillin. Concurrent use with *Augmentin* may result in increased and prolonged blood levels of amoxicillin

The concurrent administration of allopurinol and ampicillin increases substantially the incidence of rashes in patients receiving both drugs as compared to patients receiving ampicillin alone. It is not known whether this potentiation of ampicillin rashes is due to allopurinol or the hyperuricemia present in these patients. There are no data with *Augmentin* and allopurinol administered concurrently

Augmentin should not be co-administered with Antabuse® (disulfiram)

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long term studies in animals have not been performed to evaluate carcinogenic or mutagenic potential

Pregnancy (Category B): Reproduction studies have been performed in mice and rats at doses up to ten (10) times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to *Augmentin*. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed

Labor and Delivery: Oral ampicillin class antibiotics are generally poorly absorbed during labor. Studies in guinea pigs have shown that intravenous administration of ampicillin decreased the uterine tone, frequency of contractions, height of contractions and duration of contractions. However, it is not known whether the use of *Augmentin* in humans during labor or delivery has immediate or delayed adverse effects on the fetus, prolongs the duration of labor or increases the likelihood that forceps delivery or other obstetrical intervention or resuscitation of the newborn will be necessary

Nursing Mothers: Ampicillin class antibiotics are excreted in the milk, therefore, caution should be exercised when *Augmentin* is administered to a nursing woman

Adverse Reactions: *Augmentin* is generally well tolerated. The majority of side effects observed in clinical trials were of a mild and transient nature and less than 3% of patients discontinued therapy because of drug-related side effects. The most frequently reported adverse effects were diarrhea/loose stools (9%), nausea (3%), skin rashes and urticaria (3%), vomiting (1%) and vaginitis (1%)

The overall incidence of side effects, and in particular diarrhea, increased with the higher recommended dose. Other less frequently reported reactions include: abdominal discomfort, flatulence and headache

The following adverse reactions have been reported for ampicillin class antibiotics

Gastrointestinal: Diarrhea, nausea, vomiting, indigestion, gastritis, stomatitis, glossitis, black "hairy" tongue, enterocolitis and pseudomembranous colitis. Onset of pseudomembranous colitis symptoms may occur during or after antibiotic treatment (see WARNINGS)

Hypersensitivity reactions: Skin rashes, urticaria, angioedema, serum sickness-like reactions (urticaria or skin rash accompanied by arthritis/arthralgia, myalgia, and frequently fever), erythema multiforme (rarely Stevens-Johnson Syndrome), and an occasional case of exfoliative dermatitis have been reported. These reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids. Whenever such reactions occur, the drug should be discontinued, unless the opinion of the physician dictates otherwise. Serious and occasional fatal hypersensitivity (anaphylactic) reactions can occur with oral penicillin (see WARNINGS)

Liver: A moderate rise in AST (SGOT) and/or ALT (SGPT) has been noted in patients treated with ampicillin class antibiotics but the significance of these findings is unknown. Hepatic dysfunction, including increases in serum transaminases (AST and/or ALT), serum bilirubin and/or alkaline phosphatase, has been infrequently reported with *Augmentin*. The histologic findings on liver biopsy have consisted of predominantly cholestatic, hepatocellular or mixed cholestatic-hepatocellular changes. The onset of signs/symptoms of hepatic dysfunction may occur during or after therapy. Complete resolution has occurred with time

Hemic and Lymphatic Systems: Anemia, thrombocytopenia, thrombocytopenic purpura, eosinophilia, leukopenia and agranulocytosis have been reported during therapy with penicillins. These reactions are usually reversible on discontinuation of therapy and are believed to be hypersensitivity phenomena. A slight thrombocytosis was noted in less than 1% of the patients treated with *Augmentin*

Central Nervous System: Reversible hyperactivity, agitation, anxiety, insomnia, confusion, behavioral changes, and/or dizziness have been reported rarely

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* For susceptible strains of indicated organisms. *Augmentin* is appropriate initial therapy when you suspect ß-lactamase-producing organisms.

† Latest available annual data: January to December 1991.

‡ *In vitro* susceptibility does not necessarily imply *in vivo* efficacy.

Please see brief summary of prescribing information for contraindications, warnings, precautions and adverse reactions on adjacent page.

References: 1. Neu HC, Wilson APR, Gruneberg RN. Amoxicillin/clavulanic acid — a review of its efficacy in over 38,500 patients from 1979 to 1992. *J Chemother* 1993. In press. **2.** Data on file, SmithKline Beecham Pharmaceuticals. **3.** Data from the Institutes for Microbiology Research, Franklin, Tenn. **4.** Brown R, Pinkerton R, Tuttle M. Respiratory infections in smokers. *Am Fam Physician* 1987;36:133-140. **5.** Neu HC. Contribution of beta-lactamases to bacterial resistance and mechanisms to inhibit beta-lactamases. *Am J Med* 1985;79(suppl 5B):2-12.

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Articles

Aging and Left Ventricular Performance

MICHAEL H. CRAWFORD, MD, *Albuquerque, New Mexico*

A version of this paper was presented at the annual meeting of the Western Association of Physicians, Carmel, California, February 5-6, 1992.

Pathologic studies of the heart in humans have shown that with aging, hypertrophy of the endocardium and sclerosis occur, with hypertrophy the predominant finding.[1] This endothelial hypertrophy extends to the vasculature with hypertrophy of the smooth muscle layers of the blood vessels.[2] The cardiac valves show thickening along with some calcification.[3] The valve thickening is seen predominantly along the commissural fusion lines and leads to retraction of the commissures.[4] The myocardium, by light microscopy, shows no major changes. No diminution in fiber size or number is seen. Slight changes may occur in the composition of the interstitium and collagen, but these are not thought to be functionally important.[3]

Exercise studies in older persons have shown that maximal oxygen consumption ($\dot{V}O_2max$) and maximal heart rate response to exercise are reduced in this age group.[5]* In addition, the maximum end-diastolic volume and stroke volume are increased during exercise in older age groups, but the ejection fraction or the percentage of the stroke volume as a fraction of the end-diastolic volume are unchanged.[6,7] Other ejection-phase measures of left ventricular ejection performance are also unchanged. Apparently systolic ventricular performance does not change substantially with aging.

Exercise data vary considerably from one person to the next. Some 70-year-olds have the same maximum heart rate response as some 30- and 40-year-olds. Also, the ejection fraction during exercise is depressed in some elderly persons but not in others.[8] The reasons for this variability in exercise performance in the elderly are not known.

Exercise conditioning studies in the elderly have demonstrated increases in the $\dot{V}O_2max$.[5,9] In fact, the $\dot{V}O_2max$ increases more in elderly people than it does in young people during conditioning.[10] The anaerobic threshold also increases, suggesting that elderly people are able to work more efficiently. In addition, the end-diastolic volume and stroke volume increase with conditioning, but the ejection fraction remains unchanged, as do other ejection-phase indices of performance.

*See also the editorial by A. A. Ehsani, MD, "Aging and the Heart," on pages 501-502.

The structure of the heart has been postulated to correlate with some of these functional changes. Studies have shown that left ventricular hypertrophy occurs with age, associated with an increase in systolic blood pressure. Also, isometric relaxation is prolonged in the elderly, which is probably related to both reduced active relaxation of the myocardium and impaired elastic recoil.[11] Doppler studies in the elderly have shown that early diastolic filling is reduced and late diastolic filling is enhanced. Consequently, the proportion of filling in the two parts of diastole changes, but the actual left ventricular end-diastolic volume is unchanged because the enhanced late filling compensates for the decrease in early filling.[12] Again, in these resting echocardiographic studies, the left ventricular ejection performance remained the same in older persons.

This left ventricular hypertrophy and the decrease in early filling and relaxation may impair diastolic performance of the ventricle. A popular method of evaluating diastolic performance has been to examine the filling characteristics of the left ventricle by assessing mitral valve inflow velocities during diastole, but this approach does not measure volume flow. Velocity information can be converted into volume flow if the size of the mitral valve orifice during each phase of diastole is known. Because such an assessment is complex and time-consuming, most studies have focused on the velocity as an estimation of changes in volume filling.

Studies in the elderly have shown that with increasing age the peak velocity of rapid early diastolic filling (E) decreases, as does the E velocity deceleration, representing a decrease in early filling related to isovolumetric relaxation and elastic recoil. The atrial contribution to the diastolic velocity pattern, the late component (A), tends to increase with age. Thus, the ratio of diastolic velocity components (E:A) decreases with age[13] (Figure 1).

This pattern is not unique to the elderly; it can occur in anyone who has a clinical condition associated with altered diastolic function, such as changes in relaxation that might be related to catecholamine tone or responsiveness. Left atrial pressure is important as well because mitral diastolic velocities are related to pressure differences across

(Crawford MH: Aging and left ventricular performance. West J Med 1993; 159:451-454)

From the Division of Cardiology, Department of Medicine, University of New Mexico School of Medicine, Albuquerque.

Reprint requests to Michael H. Crawford, MD, Chief, Division of Cardiology, Department of Medicine, University of New Mexico School of Medicine, Albuquerque, NM 87131-5271.

ABBREVIATIONS USED IN TEXT

A = late (atrial) diastolic filling rate
E = early diastolic filling rate
$\dot{V}O_2max$ = maximal oxygen consumption

the valve. Changes in left atrial or ventricular pressure will affect the mitral inflow velocity. For example, mitral regurgitation increases the left atrial pressure and accentuates early diastolic filling. In addition, restriction and constriction of the left ventricle influence filling properties. Finally, tachycardia increases atrial velocity. Thus, estimating volume flow from measures of mitral diastolic velocity is difficult.

Another problem encountered in assessing left ventricular diastolic function in older patients is the increased incidence of coronary artery disease with aging. Coronary disease affects mitral diastolic velocity profiles. Presti and colleagues evaluated mitral diastolic velocity in patients with coronary disease before and after treadmill exercise using Doppler echocardiography of the mitral inflow region.[14] The typical resting pattern in these patients showed that the A wave was higher than the E wave, a pattern usually associated with aging. Presumably coronary artery disease can result in a stiffer left ventricle due to myocardial infarction and ischemia. All the patients had coronary artery lesions, proved by cardiac catheterization, and had chest pain, electrocardiographic changes, and wall-motion abnormalities detected echocardiographically during exercise. Yet, immediately after exercise during the time of chest pain, the E wave was higher than the A wave for these patients. This is the opposite of what would be expected, an accentuation of the typical A-greater-than-E pattern as ischemia caused the ventricle to stiffen.

Presti and associates' data showed that the E:A ratio was related to the severity of wall-motion abnormalities and left ventricular ejection performance. Presumably, exercise induced such profound ischemia that left ventricular systolic dysfunction and increased end-diastolic left ventricular pressure developed in many patients, which increased the left atrial pressure. The increase in left atrial pressure augmented the E wave and caused the diastolic velocity pattern to appear normal. This study highlights the dependence of left ventricular filling on loading conditions and ventricular systolic performance. It also emphasizes the importance of excluding coronary artery disease when evaluating changes in diastolic performance in the aged.

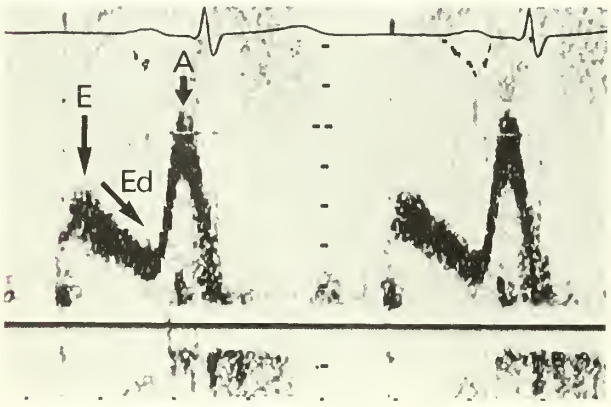

Figure 1.—The analogue display shows Doppler mitral inflow velocities during 2 cardiac cycles (note electrocardiogram at top). The early diastolic velocity (**E**), E deceleration (**Ed**), and atrial contribution to diastolic flow velocity (**A**) are shown by arrows. The distance between the dashes in the middle of the figure represents 10 cm per second. The electrocardiographic time scale is on the bottom.

Cardiac studies of the elderly in the past had several problems.[6,8,13] Most had small numbers of selected patients. Often patients were inadequately screened for coronary disease, and many had systolic hypertension. These studies were done before elevated systolic blood pressure was considered an abnormal finding in the elderly. Many of the patients in these studies were inactive, and the incidence of valvular regurgitation was unknown. These factors would influence the results of echocardiographic and Doppler measurements.

Accordingly, Shively and associates evaluated a large group of healthy elderly persons who were involved in a repeated blood donation feasibility study before they started donating blood and became anemic.[15] These patients were carefully screened for coronary artery disease, hypertension, or any other disease that might impair their ability to donate blood. They were active people, many of whom exercised regularly. They were compared with similarly screened, healthy younger people. Thus, this was a carefully selected population of healthy, active elderly persons.

The subjects were divided into three groups: a young group (25 subjects), a middle-aged group (34 subjects), and an older group (180 subjects) with a mean age of 68 years. Systolic blood pressures in this elderly group averaged 128 mm of mercury, which was not statistically different from the 120 mm of mercury found in the young group. Diastolic pressures were similar, and heart rate was not different. Echocardiographic measurements showed that the diastolic volume and ejection fraction of the older group were not significantly different from those in the young group. Also, wall thickness was not different. Four of the older subjects (2%) had left ventricular wall motion abnormalities, so the group had some patients in whom coronary disease was suspected despite careful screening. Coronary angiography was not done, nor was exercise testing. The Doppler mitral velocities in these patients showed that in the oldest group the A velocity was increased, the E velocity was decreased, and the E:A ratio was decreased. Although this was a healthy group with little demonstrable change in cardiac structure, mitral diastolic velocities suggested an alteration in diastolic performance.

Another problem in evaluating diastolic function in the elderly by Doppler echocardiography is the incidence of valvular regurgitation. The studies discussed earlier have shown valve commissural changes that may result in regurgitation and influence these measurements. Doppler

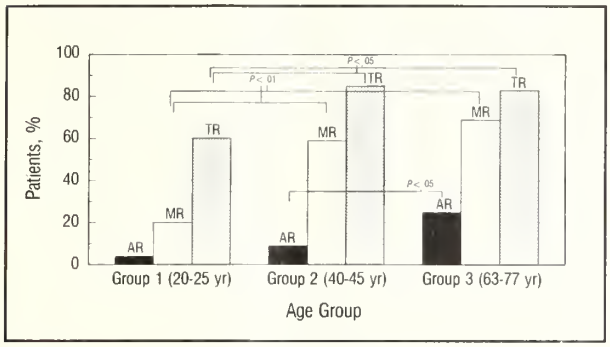

Figure 2.—The graph shows the frequency of regurgitation of the aortic (**AR**), mitral (**MR**), and tricuspid (**TR**) valves in 3 age groups. This analysis includes regurgitation judged to be trivial by color Doppler.

studies in this highly selected, healthy elderly population showed that the incidence of aortic regurgitation increases with age. The mitral and tricuspid regurgitation incidence increases until middle age and then stays about the same in the older age groups (Figure 2). The high incidence of mitral regurgitation must be considered because of its effects on Doppler measures of left ventricular filling.

For all these reasons, radionuclide angiography is believed to be more accurate for assessing diastolic performance. This technique measures volume flow by assessing changes in the radioactive count rate in the ventricle during the cardiac cycle. The count rate is reduced during systole and then increases during diastole as the ventricle fills. Peak diastolic filling occurs early and increases during atrial contraction, similar to the Doppler velocity pattern. Because accurate flow rates may be difficult to measure with a technique that samples at about 30 per second, the amount of filling (counts) during the first third of diastole is often evaluated as an estimate of early diastolic function.

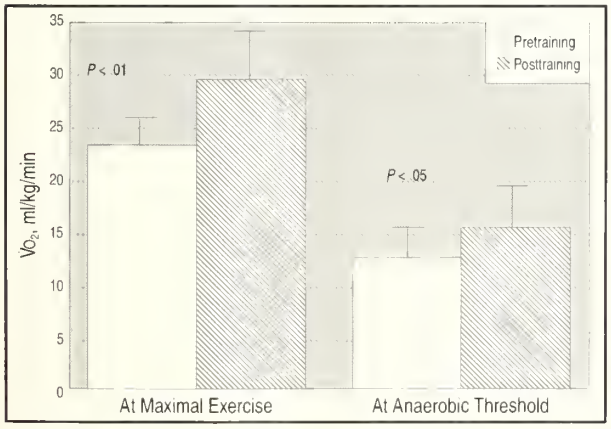

Figure 3.—Maximal oxygen consumption ($\dot{V}O_2$) and $\dot{V}O_2$ at anaerobic threshold are compared before and after training.

At the University of New Mexico (Albuquerque) School of Medicine, this technique was applied to a group of carefully selected elderly persons who were put in a training program where they received exercise training three times a week for 16 weeks. The $\dot{V}O_2$max increases, as would be expected from previous studies (Figure 3). Also, the first-third filling fraction as a measure of early diastolic filling increases significantly (Figure 4). Thus, diastolic function can be improved with training in older persons.[16]

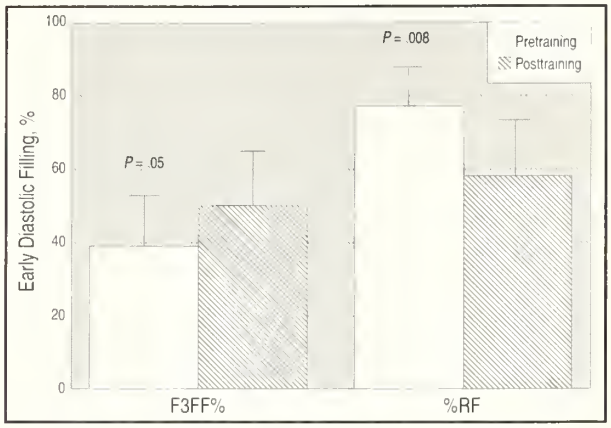

Figure 4.—Radionuclide studies of the first third of diastolic filling fraction as a percentage of total diastolic filling (**F3FF%**) and the percentage of rapid filling after initial filling (**%RF**) are compared before and after training.

In summary, cardiac structural changes related to aging in the left ventricle are minor as detected by light microscopy, and systolic function is preserved in the aged. Diastolic function seems to be impaired, and exercise capacity is reduced, but these can be improved by conditioning in elderly persons. Thus, if the effects of disease and inactivity are removed, aging may have little effect on left ventricular performance.

Questions and Answers

PHYSICIAN IN THE AUDIENCE: *A fascinating study. Could you extend it to include data on a controversial common disease phenomenon that has been postulated to have an effect on aging—that is, diabetes? Are the methods and population group you studied sensitive enough to say whether the hypoglycemic state enhances this sequence?*

ANSWER: In the studies that have been done at the University of New Mexico, anybody with diabetes has been excluded, but other studies have examined patients with diabetes and found differences in left ventricular performance indices, both in systole and diastole. Thus, there do appear to be differences in that group, which is why they were excluded from the New Mexico study. Whether these alterations are due to small vessel disease is not yet clear.

PHYSICIAN IN THE AUDIENCE: *I wonder what percentage of the general population would be excluded by the criteria that you used for selection of your older age group.*

ANSWER: That is a difficult question because it depends upon what is called the general population. Among patients in hospital, 80% are excluded because they have systolic hypertension, diabetes, or some other disease that could affect left ventricular performance. In the general population, about half are excluded. In the self-designated

healthy population that was discussed, a third are excluded. Thus, a lot of elderly people are in excellent health today.

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* * *

BETWEEN THE HEARTBEATS

Will I dream? she asks, before I push
the syringe of drugs. She tells me of her dream
the night before: the doctor was pulling
yarn from her abdomen. Red, yellow, green
it flowed down the table, across the floor,
filling the room. In one corner sat her son
coiling skeins; in another, her daughter
knitting. She sleeps now. For stories spun
between each heartbeat, I listen.
Who has loved her? What home holds her?
She weaves her dreams in silence.
The life I see, I measure
in minutes, keeping watch
over its tangled knot.

KELLY SIEVERS©
Portland, Oregon

Articles

Measles Epidemic From Failure to Immunize

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GEORGE W. RUTHERFORD, MD, *Berkeley, California*; CAROL A. PERTOWSKI, MD, *Atlanta, Georgia*;
STEPHEN H. WATERMAN, MD, *San Diego*; *and* GLORIA WOODFORD, *Berkeley, California*

During 1988 through 1990, California experienced its worst measles epidemic in more than a decade, with 16,400 reported cases, 3,390 hospital admissions, and 75 deaths. More than half of the patients were younger than 5 years; the highest incidence was among infants younger than 12 months. The epidemic centered in low-income Hispanic communities in southern and central California. The major cause of the epidemic was low immunization levels among preschool-aged children and young adults. Rates of complications, admission to hospital, and death were surprisingly high. Outbreak control efforts met with indeterminate success. Problems with these efforts included insufficient funding early in the epidemic and disappointing public response to community-based immunization campaigns. The cost of medical care and outbreak control for the epidemic is conservatively estimated at $30.9 million. Unless the level of immunization in preschool-aged children is increased, this type of epidemic will probably recur.

(Dales LG, Kizer KW, Rutherford GW, Pertowski CA, Waterman SH, Woodford G: Measles epidemic from failure to immunize. West J Med 1993; 159:455-464)

Historically, measles (rubeola) was a universal childhood disease in the United States, having an incidence rate approaching the birth rate. Following the introduction of the measles vaccine in the 1960s, the incidence of the disease fell 90%.[1] A rigorous enforcement of school and child care immunization requirements in the 1970s led to another 80% to 90% decrease in measles incidence.[2]

During the early 1980s California's measles incidence was at an all-time low of 1 to 3 cases per 100,000 population (Figure 1). From 1981 through 1987, an average of 457 cases per year were reported (range, 176 to 831). During this time, most of California's larger measles outbreaks occurred in secondary schools in which many students had entered school before immunization requirements were rigorously enforced.

In mid-1988, a different type of measles outbreak began in Los Angeles County. This outbreak was centered in low-income communities and primarily involved preschool children and young adults. The outbreak quickly grew to be an epidemic, spreading to other parts of the state and producing 3,010 cases in 1989 (10.4 cases per 100,000 population) and 12,587 cases in 1990 (42.3 cases per 100,000). In this article we describe the epidemiology of California's measles epidemic in 1988 through 1990 and public health control efforts. Similar outbreaks occurred in many other states.

Methods

Measles is a mandatorily reportable disease in California. Compliance with this requirement is judged to be good. Individual cases are reported first to the local health department on standard, state-issued forms; local health departments then report cases to the California Department of Health Services (CDHS). Disease reports contain demographic, clinical, and laboratory information as well as data on immunization history, source of infection, and measures taken to prevent secondary spread. These reports were our principal source of data.

To be included in this study, a measles case must be

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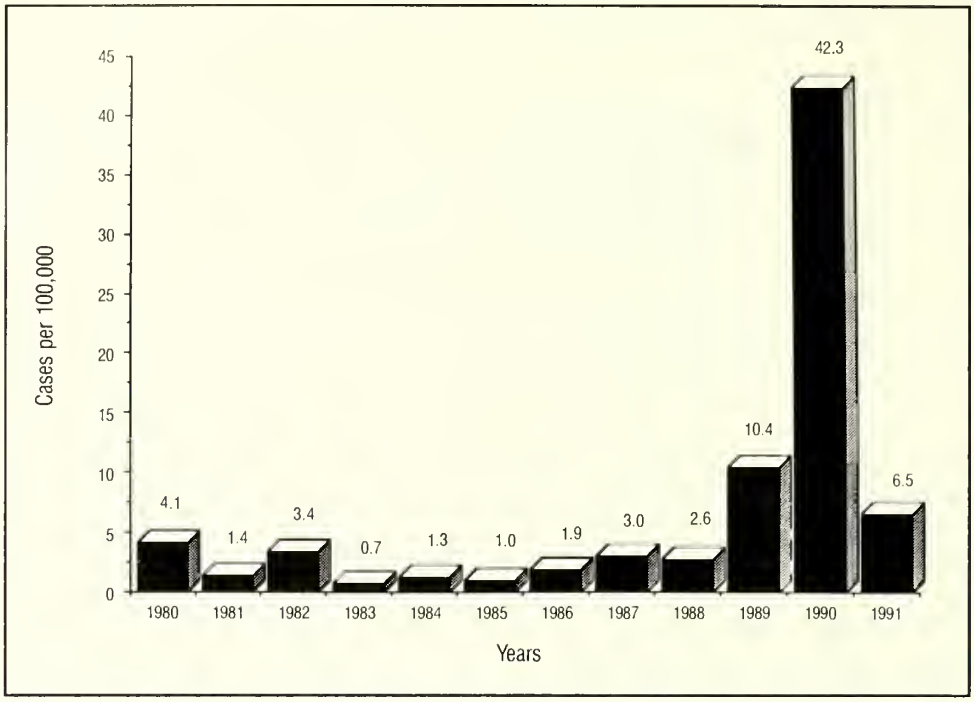

Figure 1.—Annual measles incidence rates for California increased dramatically in 1989 through 1991 from an all-time low in the early 1980s.

either laboratory confirmed or epidemiologically confirmed by virtue of meeting the federal minimum clinical criteria for measles—generalized maculopapular rash of at least three days' duration, notable fever and cough, coryza, or conjunctivitis—and being directly linked to at least one other case that meets the same clinical criteria or has been laboratory confirmed as measles.[2] Adequate measles immunization is defined as having a record showing month and year of vaccination after the first birthday. Data from case report forms were entered into a dBase 3-plus format and analyzed using Epi Info 5.01B.[3]

Results

Temporal and Geographic Course of the Epidemic

From January 1988 through December 1990, there

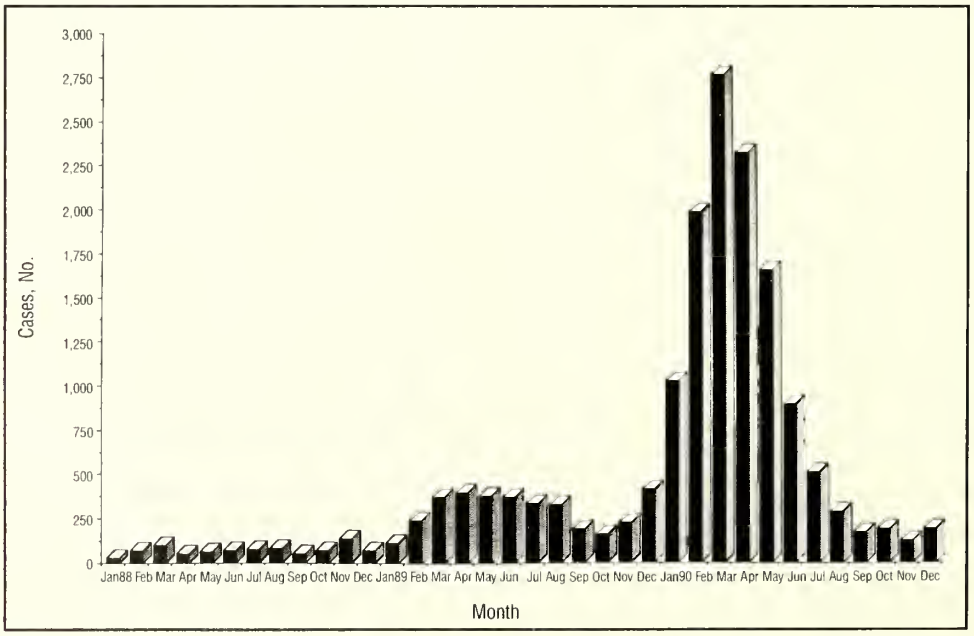

Figure 2.—The number of reported measles cases greatly increased from the spring of 1988 through the summer of 1990.

TABLE 1.—*Measles Cases by Geographic Region, California, 1988-1990*

	Measles Cases by Year					
	1988		1989		1990	
Region*	No.	%	No.	%	No.	%
Southern California	689	86.4	2,632	87.4	9,113	72.4
San Joaquin Valley	10	1.3	248	8.2	2,553	20.3
San Francisco Bay Area and Central Coast	92	11.5	99	3.3	621	4.9
Northern California and Sierras	6	0.8	37	1.2	300	2.4
Total	797	100	3,010	100	12,587	100

*Southern California: Imperial, Los Angeles, Orange, Riverside, San Bernardino, San Diego, Santa Barbara, and Ventura counties. San Joaquin Valley: Fresno, Kern, Kings, Madera, Merced, San Joaquin, Stanislaus, and Tulare counties. San Francisco Bay Area and Central Coast: Alameda, Contra Costa, Marin, Monterey, Napa, San Benito, San Francisco, San Luis Obispo, San Mateo, Santa Clara, Santa Cruz, Solano, and Sonoma counties. Northern California and Sierras: all other counties.

were 16,400 cases of measles reported to the CDHS. Of these, 1,948 (12%) were laboratory confirmed. Figure 2 depicts cases according to month of rash onset, and Table 1 shows the regional distribution of cases.

In early 1988, most measles cases being reported to the CDHS were linked to secondary schools and colleges, as had been the pattern in previous years. In May and June 1988, a new pattern of measles outbreak appeared in Los Angeles County; young children in low-income communities suddenly became the predominant population affected. In the ensuing months, increased measles incidence appeared in other southern California counties. By early 1989, a measles epidemic was definitely under way, with the disease spreading throughout southern California and also appearing in the San Joaquin Valley. In late 1989 and early 1990, the epidemic accelerated in both southern California and the San Joaquin Valley, with localized outbreaks occurring in northern California. The epidemic peaked in March and April 1990 (2,757 and 2,313 cases, respectively). The incidence decreased dramatically in the second half of 1990 (Figure 2) but remained above pre-epidemic levels until the spring of 1991. A total of 1,963 cases occurred in 1991, with 1,140 and 611 cases being reported in the first two quarters of the year, respectively, and 212 cases in the second half of the year. The case total for 1992 was 61, an all-time low.

While the 1988 incidence and case total were not significantly different from those of 1987, the initial outbreaks and transmission patterns that led to the notably increased 1989 and 1990 caseload began in mid-1988. Thus, 1988 is included as the first year of the epidemic.

Age, Sex, and Race or Ethnicity of Cases

Table 2 shows California's measles cases and incidence by age for the 1980s. From 1988 through 1990, more than half of patients were of preschool age, compared with 30% in the pre-epidemic period. Both before and during the epidemic, infants younger than 12 months had the highest incidence, followed by children aged 1 to 4 years. Figure 3 shows the age distribution of cases in infants and children younger than 2 years for the epidemic period.

At some points in the epidemic the preponderance of preschool-aged cases was particularly striking. For example, in Los Angeles County during the summer of 1988, more than 75% of reported cases were in children younger than 5; most of them were Hispanic. Also, in two local outbreaks affecting Samoan and Southeast Asian children, 65% and 87% of patients, respectively, were younger than 5 years.

Although race and ethnicity were not recorded for many cases, tabulation by surname indicated that 40% of disease instances were in persons of Hispanic and 5% were in persons of Asian or Pacific Island ancestry. Race was recorded for all Los Angeles County patients (6,286); among these, 10% were African Americans.

TABLE 2.—*Age Distribution and Incidence Rates for California Measles Cases, 1980-1990*

	Measles Cases by Year								
	1980-1987			1988			1989-1990		
Age Group, yr	No.	%	Average Annual Incidence Rate*	No.	%	Average Annual Incidence Rate*	No.	%	Average Annual Incidence Rate*
<1	503	12.2	14.3	128	16.1	31.0	3,081	19.8	363.1
1-4	738	17.9	5.4	232	29.1	12.1	5,181	33.2	131.3
5-9	523	12.7	3.7	65	8.2	2.9	1,297	8.3	29.2
10-19	1,476	35.8	4.9	219	27.5	5.7	2,207	14.1	27.4
≥20	776	18.8	0.5	153	19.2	0.8	3,787	24.3	9.0
Unknown	112	2.7	--	--	--	--	50	0.3	--
Total	4,128	100	2.0	797	100	2.8	15,603	100	26.2

*Cases per 100,000 population. For multiple-year periods, midpoint population estimates were used.

Figure 3.—Cases of measles younger than 2 years were highest among 8- to 12-month-old infants during the 1988-1990 epidemic.

Immunization Status

Only 12% of patients aged 1 to 4 years had been immunized against measles, whereas 45% of 5- to 19-year-olds had been immunized. The remainder of the school-aged patients had either legally allowed exemptions to the school immunization requirement or, more often, school records showing the measles immunization missing or inadequately documented. Only 4% of patients older than 20 years had been immunized.

Among unimmunized patients aged 12 months and older, 1.6% had religious or philosophical beliefs against immunization and 0.2% reported a medical contraindication to immunization. The remaining 98% simply had not been immunized or could not document immunization.

Source of Infection

The source of infection was identified for only 21% of patients. Of these, 62% were infected in their own household or by a neighbor or friend; 16% were infected in medical care facilities; 14% were infected in child care centers, schools, or colleges; and 8% were infected in jails, prisons, or other detention facilities. For patients acquiring their infection at a medical care facility, the facility was a hospital three fourths of the time. A third of medical facility-transmitted cases involved patients infected in emergency departments. Only 0.8% of cases were thought to have been imported from outside California; 82% (106 cases) of these were from Mexico.

Complications, Hospital Admissions, and Deaths

Table 3 shows the frequency of selected measles complications by age group for 1987 through 1990. The data for 1987 are representative of previous years. Pneumonia and diarrhea were the most frequently reported complications. Complications were generally less frequent in school-aged children than for preschool-aged children or adults. In all age groups, pneumonia and diarrhea were more common than reported in pre-epidemic years.

For the pre-epidemic years 1981 through 1987, only summary data on admissions to hospital were available: 2.4% of 4,132 cases required hospital admission during this time. In contrast, more than 20% of cases reported in 1988-1990 required hospital admission (Table 4).

From 1988 through 1990, 75 patients with measles died, for an overall case-fatality rate of 0.5% (Table 5). Of these patients, 89% had pneumonia and 15% had encephalitis (4% had both). The most common cause of death was primary measles pneumonia leading to respiratory failure. The case-fatality rate for children aged 5 to 19 years (0.1%) was five to six times lower than that for preschool-age children and adults. Case-fatality rates by racial or ethnic group were as follows: Hispanic surname, 0.4%; Asian or Pacific Islander surname, 2.5%; all others, 0.3%. The high case-fatality rate among Asians or Pacific Islanders relates to two specific outbreaks that are discussed below.

Institutional Outbreaks

Although most cases in the epidemic were community acquired, outbreaks erupted in several institutions.

Schools and colleges. More than 3,500 cases (21%) involved schools. The vast majority of school-related incidents involved 1 to 3 cases, indicating that transmission in schools was not a major cause of the epidemic. Five junior and senior high schools had outbreaks of 10 to 20 cases each. In 1988 a multiple-school outbreak in Orange County resulted in 43 student cases; this outbreak primarily involved secondary schools. Eight colleges had out-

TABLE 3.—*Measles Case Complications by Age Group, California, 1987 and 1988-1990*

Complication by Age Group, yr	Measles Cases by Year: 1987* Cases, No.	1987* Complication Present Na.	1987* Complication Present %	1988-1990 Cases, Na.	1988-1990 Complication Present Na.	1988-1990 Complication Present %	P Value
Pneumonia							
<1	57	0	0.0	3,209	285	8.9	.008
1-4	138	2	1.5	5,413	492	9.1	.002
5-19	426	4	0.9	3,788	145	3.8	.002
≥20	125	3	2.4	3,940	338	8.6	.01
All ages	746	9	1.2	16,350	1,260	7.7	<.001†
Diarrhea							
<1	57	3	5.3	3,209	472	14.7	.05
1-4	138	6	4.4	5,413	727	13.4	.002
5-19	426	24	5.6	3,788	370	9.8	.02
≥20	125	8	6.4	3,940	551	14.0	.02
All ages	746	41	5.5	16,350	2,120	13.0	<.0001†
Otitis Media							
<1	57	8	14.0	3,209	237	8.0	.13
1-4	138	14	10.1	5,413	411	7.6	.27
5-19	426	4	0.9	3,788	66	1.7	.22
≥20	125	0	0.0	3,940	18	0.5	1.00
All ages	746	26	3.5	16,350	732	4.5	.55†
Encephalopathy							
<1	57	0	0.0	3,209	5	0.2	1.00
1-4	138	0	0.0	5,413	11	0.2	1.00
5-19	426	0	0.0	3,788	2	0.1	1.00
≥20	125	2	1.0	3,940	8	0.2	.04
All ages	746	2	0.3	16,350	26	0.2	.49†

*Information was available for only 92% of 1987 cases.
†Mantel-Haenszel summary χ^2 *P* value.

breaks ranging from 2 to 38 cases per college (127 cases total).

Detention facilities. A total of 23 outbreaks occurred in jails, prisons, or juvenile halls—1 in 1988, 4 in 1989, and 18 in 1990. These outbreaks ranged from 2 to 103 cases, with a combined total of 278 cases (1.6% of all epidemic cases). Of these, 98% (271 cases) were inmates. Four inmates died of respiratory complications, yielding a case-fatality rate of 1.5%.

Medical care facility cases. Of the epidemic cases, 554 patients (3.4%) were known to have acquired their infection in medical care facilities. During the 27-month period from January 1988 through March 1990, 157 patients (46%) with infection acquired in medical care facilities were facility staff members. Because the epidemic caseload outstripped investigative resources by the spring of 1990, occupation was not determined during most of 1990, and medical staff cases could not be identified for this period.

Of the 157 medical facility staff members infected, 5% (8 cases) were 15 to 19 years old, 50% (76 cases) were 20 to 29 years, 40% (65 cases) were 30 to 39 years, and 5% (8 cases) were 40 or older. Nurses made up 26% (41 cases), 17% (27 cases) were physicians, and 10% (15 cases) were laboratory or radiology staff members; the remaining 47% (74 cases) had a variety of other jobs. For 84% of medical facility staff cases, the known or presumed exposure site was a hospital; 17% of these were thought to have been infected in the emergency department. Only 4% of the infected staff members had a documented history of measles immunization. Some health care workers continued working during their illness prodrome, exposing other staff and patients, but detailed information documenting staff-to-staff or staff-to-patient transmission is not available.

TABLE 4.—*Measles Cases Admitted to Hospital by Age Group, California, 1988-1990*

Age Group, yr	Measles Cases, No.	Admitted to Hospital No.	Admitted to Hospital %
<1	3,209	782	24.4
1-4	5,413	1,232	22.8
5-19	3,788	448	11.8
≥20	3,940	933	23.7
Unknown	50	0	0.0
Total	16,400	3,395	20.7

TABLE 5.—*Age-Specific Death Rates for California Measles Cases, 1980-1987 and 1988-1990*

	Measles Cases by Year						
	1980-1987			1988-1990			
		Deaths			Deaths		
Age Group, yr*	Cases, No.	No.	%	Cases, No.	No.	%	P Value
<1	503	0	0.0	3,209	17	0.6	.10
1-4	739	2	0.3	5,413	34	0.6	.31
5-19	2,003	0	0.0	3,788	3	0.1	.56
≥20	776	1	0.1	3,940	21	0.5	.16
Unknown	12	0	0.0	50	0	0.0	--
All ages	4,033	3	0.07	16,400	75	0.5	.01†

*For the years 1980 through 1986, cases were tabulated by slightly different age groups (≤14 months, 15 months through 4 years, 5 through 18 years, and ≥19 years). This table does not reflect these grouping differences.

†Mantel-Haenszel summary χ^2 P value.

The severity of illness for medical staff cases paralleled that observed for adult cases overall. Four workers with pneumonia required ventilatory support, and encephalitis developed in two, one of whom was left quadriplegic. Three health care workers died.

Outbreaks With Exceptional Mortality

During the course of this epidemic, two outbreaks had exceptionally high case-fatality rates. The first of these was an outbreak of 61 cases among Samoan children in Los Angeles and Orange counties in the winter and early spring of 1989. Transmission occurred primarily within and among extended families and at church gatherings. None of the patients old enough to have received measles vaccine had been immunized. Pneumonia developed in 24 (40%) of these children, and 6 (10%) died. Case-fatality rates by age group were 10% for infants younger than 12 months (1 of 10 patients) and 17% for patients aged 1 to 4 years (5 of 29 patients). All 22 patients aged 5 years and older survived.

The second outbreak occurred between mid-summer 1989 and late spring of 1990 among Southeast Asian children in Fresno County, with secondary spread to other Southeast Asian communities in nearby Stanislaus, San Joaquin, and Sacramento counties. Of the 363 cases involved, 290 (80%) were in Hmong children. Of these children, 78 (27%) were infants younger than 12 months, 174 (60%) were 1 to 4 years old, and almost all of the remaining 13% were aged 5 to 9 years. Of note, 10% of the preschoolers and 55% of the school-aged children had had measles immunization at 12 months of age or older. Of these infants and children, 30% were admitted to hospital and 13 died (age range 5 months to 2½ years), yielding a case-fatality rate of 3.6%. All deaths were due to pneumonia with respiratory failure.

Epidemic Control Efforts

Both the CDHS and local health departments pursued multifaceted epidemic control programs, although specific activities varied according to the epidemic's local characteristics.

Investigation and follow-up of individual cases. Individual case investigation and follow-up were undertaken to identify household and other close contacts and to isolate and administer vaccine or immune globulin to those known or presumed to be susceptible. As the number of cases increased in heavily affected areas, this labor-intensive activity was given lower priority, with resources instead being focused on community-wide control efforts.

Institutional outbreak control programs.

- *Schools and child care centers*—All unimmunized students were identified and notified that they must be immunized immediately or be excluded from school attendance. In 350 schools and child care centers that had measles cases or were threatened by measles outbreaks, approximately 6,000 (2.1%) of 280,000 pupils were identified as unimmunized and received exclusion notices. In at least 11 secondary school outbreaks, voluntary (9 schools) or mandatory (2 schools) reimmunization programs were undertaken for pupils who had been immunized at age 12 to 14 months (because of the lower efficacy of vaccination at this early age[4,5]) or who had received only one dose of measles vaccine. At least 12,000 pupils were reimmunized at special clinics held at or near these schools.
- *Colleges*—At least 11,500 students and staff members were immunized in voluntary or mandatory immunization programs at colleges having measles outbreaks. Several of these programs included voluntary reimmunization of students who had a history of only one measles vaccine dose.
- *Detention facilities*—Mandatory or voluntary immunization programs for inmates and staff members were held in 36 jails, prisons, or other detention facilities with measles outbreaks; at least 46,000 persons were immunized through these programs.
- *Health care facilities*—Many hospitals and medical clinics conducted one or more of the following: immunization of exposed, susceptible patients and staff; voluntary or mandatory immunization programs for staff; and voluntary measles immunization for all children aged 1 through 4 years brought into the facility for any reason (unless immunization was medically contraindicated or the child had documented prior immunization).

Community-wide outbreak control programs.

- *Immunization schedule changes*—In 11 counties

having measles outbreaks, the recommended standard age for measles-mumps-rubella immunization was lowered from 15 to 12 months of age. In 1990 all public immunization clinics in the nine most heavily affected counties began administering monovalent measles vaccine to all infants at 6 to 11 months. More than 36,000 infants were vaccinated between mid-1990 and early 1991. Parents of these infants were instructed to bring them back for their routine dose of vaccine at age 15 months.

• *Expansion of public immunization clinic services*—Measles immunization services in local health department clinics and in many nonprofit community clinics were augmented (as resources allowed) by increased staffing and hours of clinic operation. In addition, a variety of special immunization clinics were held. Door-to-door residential immunization programs were conducted in some high-risk areas.

• *General publicity*—Multilingual messages urging families to immunize their children were widely disseminated, using general news releases; presentations in churches, English-as-a-second-language classes, and community centers; mailings to Aid to Families with Dependent Children and Medi-Cal (California's Medicaid) clients; and distribution of leaflets or posters in markets and other retail outlets, libraries, laundromats, farm labor camps, churches, community centers, Women Infants and Children food supplementation clinics, medical care facilities, welfare offices, and other sites.

It is not possible to evaluate precisely the effect of community-wide control efforts because no outbreak was allowed to continue unchecked to provide a basis for comparison. The fact that the epidemic persisted for three years underscores the difficulty that these outbreak control efforts had in combatting the epidemic.

Cost of the Epidemic

Based on a 1989 Los Angeles County survey finding that measles hospital admissions averaged five days at a mean cost of $1,200 per day,[6] the cost for the 3,390 measles hospital admissions in 1988 through 1990 was estimated at $20.34 million. Assuming that all 16,400 reported cases involved at least one outpatient visit each, at an average cost of $80, the total outpatient medical care cost is estimated at $1.31 million.

Comparing observed with expected usage of CDHS-supplied measles vaccines in public programs during the epidemic period indicates that more than 370,000 vaccine doses were used in epidemic control programs, for a vaccine cost of more than $5 million. Other costs included an estimated $2.0 million spent by local health departments for extra staffing of special immunization clinics, case investigation, and other disease control activities and $2.2 million in state funds specifically appropriated in 1990 for immunization clinic expansion.

Total expenditures for direct medical care and outbreak control activities are conservatively estimated at $30.9 million. This figure is certainly an underestimate, and it does not include indirect costs such as lost income and productivity by working adults who became ill or who missed work to care for ill children, the lifetime income and productivity loss for the 75 persons who died, and the productivity loss to local health departments and medical care facilities resulting from diverting staff from other activities to help with epidemic control.

Discussion

Campaigns to implement and rigorously enforce school immunization laws and to strengthen measles surveillance and outbreak control efforts were successfully executed across the United States in the late 1970s. As a result, many people hoped that indigenous measles transmission would be eliminated from the United States in the early 1980s. Clearly this has not happened, and California's epidemic in 1988 through 1990 was part of a larger national epidemic.[2]

In reviewing the data presented here, it is important to recognize their limitations. Measles cases were ascertained by a passive surveillance system, and substantial underreporting of cases almost certainly occurred. Only a few cases were laboratory confirmed, so it is likely that some illnesses other than measles were mistakenly included among the epidemiologically confirmed cases. Further, among reported cases, not all of the information sought on case report forms was consistently gathered as the caseload overwhelmed local health department resources in the more heavily affected areas. Despite these limitations, the principal features and implications of the epidemic are clear.

During the 1980s, measles outbreaks in the United States continued to occur in two principal forms: secondary school outbreaks, in which most patients were reported as having been immunized at or about 12 months of age, and outbreaks affecting unimmunized preschool-aged children in low-income communities.[7]

The number of cases occurring among toddlers (2,631 patients aged 6 to 11 months and 3,014 patients aged 12 to 23 months) underscores both the need for a vaccine that is more effective in small infants and the need for young children to be vaccinated as soon as they reach immunization age. A measles vaccine that could be given routinely with a high level of efficacy at 9 months of age or younger, such as the Edmonston-Zagreb strain vaccine currently under evaluation,[8] may prove to be helpful in addressing the former need, while the latter requires that greater efforts be directed toward achieving universal immunization. Based on the number of patients having no history of measles vaccination, as many as 65% of the 16,400 reported cases and deaths—that is, 10,660 cases and possibly 49 deaths—might have been prevented by universal immunization.

The site of exposure was not definitively identified for most cases, although most transmission appeared to occur outside of institutions. Next to households, medical care facilities were the most commonly identified transmission site. A case-control study undertaken in a large inner-city hospital in Los Angeles County revealed that unimmunized preschool-aged children had a fivefold increased risk of measles developing in the two weeks after visiting

the emergency department.[9] Another Los Angeles-based study documented patient-to-staff and patient-to-patient measles transmission.[10] These data underscore the need for medical care facilities, especially emergency departments and acute care clinics, to aggressively adhere to disease prevention guidelines. The fact that 23% of the medical staff members infected were born before 1957 also illustrates that medical facility measles immunization policies should not be restricted solely to young adults.[10] Indeed, medical care facilities must ensure that all health care workers are immune to measles.

A substantial number of cases did occur in schools despite the fact that only about 2% of California's primary and secondary school students were not immunized. If measles vaccine has a 95% efficacy in persons immunized at age 15 months[11] and 98% of students have received one vaccine dose, then only 93% of pupils will be immune. Because vaccine efficacy is slightly lower in persons immunized at age 12 to 14 months,[4,5,12] the overall school immunity rate may be less than 93% if a substantial proportion of pupils have been immunized at age 12 to 14 months. This is important because previous investigations have demonstrated that more than 95% of the population in secondary schools must be immune to prevent outbreaks of measles once infection has been introduced.[13] This again underscores the need for universal immunization.

One of the questions that arose during the epidemic was the efficacy of the measles vaccine. Three lines of evidence indicate that its efficacy was high. First, despite the many introductions of measles into schools that must have occurred (over 3,500 cases in persons aged 5 to 18 years), few large school outbreaks followed. Most cases in school-aged children resulted in very little, if any, school transmission. Only a handful of school outbreaks with more than three cases are known to have occurred. Second, a rough estimate of measles vaccine efficacy (VE) in school pupils can be made using the formula:

$$VE(\%) = [(PPV - PCV)/PPV(1 - PCV)] \times 100$$

where PPV is the proportion of the population vaccinated and PCV is the proportion of cases vaccinated.[14] Surveys of kindergarten entrants and older pupils conducted annually in California over the past decade indicate that 97% to 98% of pupils in grades kindergarten through 12 have been immunized against measles. Of the school-aged measles patients in this epidemic, 45% had been immunized. Using these two values in the above formula results in a measles vaccine efficacy estimate of more than 98%. Third, a study undertaken in California in 1990 comparing infection rates between immunized and unimmunized preschool-aged household contacts of measles cases demonstrated a vaccine efficacy point estimate of 95% (95% confidence interval, 89% to 97%).[11] Thus, it is clear that the vaccine was working well, and the major factor contributing to this epidemic was that too few children had been vaccinated.

A remarkable feature of this measles epidemic was the high frequency of serious illness and complications compared with what has been recorded for other measles epidemics in developed countries.[15,16] And the actual complication rate may have been higher than reported here. For example, a special investigation of children aged 1 to 5 years in late 1989 and 1990 found rates of complications higher than those shown in Table 3; that investigation found complication rates for pneumonia of more than 10%, for diarrhea of 5%, and for otitis media of more than 35%.[11]

Measles is generally more severe in infants, young children, and adults than in school-aged children[16]; these higher-risk age groups made up a greater proportion of California's cases from 1988 through 1990 than in earlier years. Tables 3 and 5 indicate that for pneumonia, diarrhea, and death, age stratification of cases did not eliminate the relatively increased disease severity. Changes in the racial or ethnic composition of cases might partially account for the increased illness severity. Unexplained high case-fatality rates were recorded among both Samoan (10%) and Hmong children (3.6%). If the 19 Samoan and Hmong fatalities are subtracted from the 75 total deaths, the age-stratified summary case-fatality rate for the epidemic period remains significantly higher than that for the period from 1980 through 1987 (Mantel-Haenszel summary χ^2 P value = .007).

Evaluating the role of race or ethnicity as a factor in the epidemic's increased severity is difficult because this variable was not recorded on most case reports for most of the 1980s. Surnames were recorded, however, so, as a surrogate for actual race or ethnicity data, comparisons were made for Hispanic surnames. This is a reasonable surrogate in view of the fact that 80% of California's Hispanic population immigrated from Mexico or was descended from Mexican immigrants.[17] Complication rates among measles patients with Hispanic surnames, stratified by age, are compared for 1987 and 1988 through 1990 in Table 6. As with cases of all racial or ethnic groups combined (Table 3), pneumonia and diarrhea rates were significantly higher for Hispanic patients during the epidemic. Age-specific hospital admission data for Hispanic cases were compared for 1987 and 1988 through 1990 (Table 7). For epidemic-period cases, 23% required admission to hospital compared with 3.7% of the 1987 cases. Differences in age composition do not account for this difference. Likewise, in the eight-year period 1981 through 1987, only two Hispanic measles patients are known to have died, compared with 27 of the 6,524 Hispanic cases occurring in 1988 through 1990. Thus, for Hispanic persons, most indices of illness severity rose during the epidemic, which suggests that a change in racial or ethnic composition of the population is not the major explanation for the observed increase in illness severity.

Other possible explanations for the apparent increased measles severity include underreporting of mild cases during the epidemic and underreporting of measles complications before 1988. Currently available data do not allow us to clearly corroborate or refute either possibility. The fact that otitis media, unlike pneumonia and diarrhea,

TABLE 6.—*Complications by Age Group for California's Hispanic Measles Cases, 1987 and 1988-1990*

	Measles Cases by Year						
	1987*			1988-1990			
		Complication Present			Complication Present		
Complication and Age Group, yr	Cases, No.	No.	%	Cases, No.	No.	%	P Value
Pneumonia							
<1	15	0	0.0	1,755	139	7.9	.62
1-4	40	1	2.5	2,466	233	9.5	.17
5-19	38	0	0.0	1,250	54	4.3	.19
≥20	16	1	6.3	1,030	72	7.0	.69
All ages	109	2	1.8	6,501	498	7.7	.05†
Diarrhea							
<1	15	1	6.7	1,755	259	14.8	.71
1-4	40	1	2.5	2,466	360	14.6	.03
5-19	38	0	0.0	1,250	132	10.7	.03
≥20	16	1	6.3	1,030	144	14.0	.71
All ages	109	3	2.8	6,501	895	13.8	.002†
Otitis Media							
<1	15	1	6.7	1,755	147	8.4	1.00
1-4	40	1	2.5	2,466	199	8.1	.37
5-19	38	0	0.0	1,250	23	1.8	1.00
≥20	16	1	6.3	1,030	4	0.4	.07
All ages	109	3	2.8	6,501	373	5.7	.44†
Encephalopathy							
<1	15	0	0.0	1,755	4	0.2	1.00
1-4	40	0	0.0	2,466	6	0.2	1.00
5-19	38	0	0.0	1,250	0	0.0	Undefined
≥20	16	0	0.0	1,030	3	0.3	1.00
All ages	109	0	0.0	6,501	13	0.2	.44†

*Information was available for only 92% of 1987 cases.
†Mantel-Haenszel summary χ^2 *P* value.

was not reported more frequently in 1988 through 1990 (Table 3) seems to argue against changes in reporting of cases or complications as an explanation. Further, measles case reporting among medical facility staff should be fairly complete, yet the complication and case-fatality rates for this population were also notably high during 1988 through 1990.

In addition to the above-noted factors, constrained access to medical care among low-income Hispanic persons may have contributed to the occurrence of complications and to the increased disease severity. Unfortunately, available data do not allow us to evaluate this issue. Further investigation in this regard might be productive in answering questions about the importance of ready access to medical care for diseases like measles.

Local and state health department efforts to control this epidemic had an indeterminate effect. Constraints hampered each type of control measure. For example, the size of the epidemic overwhelmed the capability of local health departments to do detailed follow-up of individual cases, although individual case investigation (to identify and immunize susceptible contacts) is an inherently weak

TABLE 7.—*Hospital Admissions by Age Group for California's Hispanic Measles Cases, 1987 and 1988-1990*

	Measles Cases by Year						
	1987*			1988-1990			
		Hospital Admissions			Hospital Admissions		
Age Group, yr	Cases, No.	No.	%	Cases, No.	No.	%	P Value
<1	15	0	0.0	1,755	428	24.4	.03
1-4	40	2	5.0	2,466	621	25.2	.003
5-19	38	0	0.0	1,250	175	14.0	.01
≥20	16	2	12.5	1,030	268	26.0	.39
All ages	109	4	3.7	6,501	1,492	23.0	<<.01*

*Information was available for only 92% of 1987 cases.
†Mantel-Haenszel summary χ^2 *P* value.

strategy for a disease as infectious as measles, and particularly when exposure so often occurs in anonymous group settings, such as supermarkets, buses, and the like. Control efforts for institutional outbreaks dealt with more readily identifiable and accessible target populations, but jail and prison disease outbreaks presented other difficulties. Because inmates did not have immunization records available and because the often rapid turnover in these institutions provided a continuing supply of susceptible persons, the only effective control measure was mass immunization of all current and incoming inmates for at least one incubation period after the last measles patient was removed. Such efforts were costly in both vaccine and staff time. Initial high inmate refusal rates in some of the voluntary immunization programs necessitated mandatory immunization programs for these persons.

Because most measles transmission in this epidemic appeared to be occurring in the community at large, community-wide efforts were a major containment strategy. Substantial problems were encountered in this regard, however. Resource limitations, in particular, restricted activities at both the state and local levels.

From the epidemic's beginning in 1988 through the spring of 1990, the CDHS had recurring shortages of funds to purchase vaccine. This limited the agency's outbreak control efforts and precluded administering monovalent measles vaccine to 6- to 11-month-old infants in public immunization clinics in high-incidence areas until late in the epidemic. In addition to vaccine funding problems, staffing limitations in local health departments restricted the ability to expand immunization services. In the late winter and spring of 1990, as the epidemic reached its peak, the CDHS was able to focus the attention of the California legislature on this problem, resulting in supplemental appropriations of $6 million to procure additional measles vaccine and $2.2 million to augment immunization activity by local health departments and nonprofit community clinics.

The second major problem encountered with community-wide epidemic control efforts was difficulty motivating parents in target populations to have their children immunized. Special immunization campaigns repeatedly produced disappointing results despite extensive multilingual publicity efforts. The best responses occurred in communities that had just been inundated with news stories about measles deaths. The farther away these messages were, either in time or geographically, the poorer the public response to immunization campaigns.

It must be recognized that even with adequate resources and good public response to immunization campaigns, the control of measles epidemics is difficult. Measles is a highly contagious, rapidly spreading infection that has repeatedly demonstrated its ability to erupt even in the presence of high population immunity levels.[5,13,18] Over the past several years, measles epidemics similar to California's have arisen and persisted for prolonged periods in other parts of the country.[7,19,20] Indeed, none of the epidemic control efforts tried in California or elsewhere in the United States have proved to be rapidly and consistently successful in halting widespread outbreaks of this disease.

The key to preventing future measles epidemics is raising immunization levels among preschool-aged children, especially in low-income communities. Unfortunately, improvement in this regard has been elusive. Surveys conducted in California[21] and elsewhere in the United States[22] indicate that only 70% of children have been immunized against measles by their second birthday, with this figure being as low as 55% in low-income communities. This situation has persisted despite a wide variety of efforts made by government agencies, the private medical sector, and volunteer groups.[22] To improve this situation substantially, we need a measles vaccine that is effective in infants younger than 12 months, better accessibility of immunizations for low-income families, and more effective methods of motivating parents to have their young children immunized. Measles outbreaks and epidemics such as this one will continue to occur unless population immunization rates can be increased and maintained at essentially universal levels.

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Conferences and Reviews

Amnesia in Medical Practice

Discussant
JAMES A. TULSKY, MD

This discussion was selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from a transcription, it has been edited by Nathan M. Bass, MD, PhD, Associate Professor of Medicine, under the direction of Lloyd H. Smith Jr, MD, Professor of Medicine and Associate Dean in the School of Medicine.

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HOMER A. BOUSHEY, MD*: *The topic chosen for discussion in this conference involves the impairment of memory, a common problem among the elderly. The disorder that James A. Tulsky, MD, will discuss differs from most forms of memory loss in the abruptness of its occurrence and its reversibility.*

JAMES A. TULSKY, MD†: To introduce a discussion of amnesic syndromes, I present an illustrative case:

Case Presentation

The patient, a 71-year-old male physician without any serious medical problems, awoke one morning to a world that seemed "unreal." Despite this feeling of detachment, he went to the hospital, entered the operating room, and performed a scheduled vaginal hysterectomy. He completed the procedure in 45 minutes and without complications. He dictated his operative report and then looked in on several patients. Although no mishaps occurred, to this day he has no recollection of performing the operation.

The obstetrics-gynecology resident who scrubbed on the case noticed that something was wrong, as the surgeon repeatedly announced each step of the operation. For example, he said, "Now I am taking the cardinal ligament," over and over again while doing that procedure. This behavior was unusual, even for this man who was well known to teach during surgery.

His office nurse also began to suspect that something was wrong. Every hour that morning he called her up and asked when his first patient was scheduled. She patiently told him that his first appointment was a new patient scheduled at noon. Because his office hours always started at noon, these calls seemed unnecessary and bizarre. At 1 PM he strolled into his office an hour late, unaware that anything was wrong. His nurse noticed that he looked "detached." He saw all the patients on his roster that afternoon, but spent little time with them and appeared preoccupied. His nurse feared he was having a stroke and called an internist who worked in a nearby office. He did not examine the patient but reassured the nurse that everything was probably OK and asked that she call him back if this behavior continued.

At the end of the day the patient left his office and went to retrieve his car at the parking garage. One of the attendants found him wandering aimlessly, for he could not recollect where he had parked. His wife drove downtown, helped him find his car, and took him home. By this time, he was acting normally. His personal physician examined him two days later and found no abnormalities.

Two years later a similar episode occurred. This time the physician was giving a lecture to a group of internal medicine residents. He last remembers walking into the conference room and seeing someone "with a beard." Although he does not recall giving the talk, he did receive a complimentary thank you note a week later. When he arrived at the office his nurse recognized his behavior from two years earlier. She called his son, a medical student in psychiatry rotation at a nearby hospital, and asked him to come to the office. "Your father's having one of his 'spells' again," she said. When the son arrived, the patient was perplexed and asked, "What are you doing here?"

"I came down because your nurse called and said you weren't feeling well," replied the son.

"I feel fine," responded the patient emphatically. Then, with an expression on his face of just noticing his son, he asked, "What are you doing here?"

After this sequence was repeated several times, the patient changed topics and asked, "Where's Mother?"

"She's in Israel; she'll be coming back tomorrow," answered the son.

With an expression of shock, the physician replied, "Israel? How long has she been there?"

The son informed him, "She left three weeks ago."

Exasperated, the patient declared, "Israel. She's been gone three weeks? Oh, my, something is very wrong." Then, after a slight pause and again with a fresh expression, he asked, "Where's Mother?"

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ABBREVIATIONS USED IN TEXT

CT = computed tomography
MRI = magnetic resonance imaging
NMDA = *N*-methyl-D-aspartate

This last exchange was repeated at least ten times. As hard as he tried, the son could not break the cycle. Over the next hour and a half, however, the patient's mentation began to clear, and he was able to remember what was told to him. He recognized that his memory was not normal and repeated again and again, "God, I can't believe what happened."

Discussion

This patient suffered from an episode of transient global amnesia. As would be expected from this bizarre, poorly understood, and benign disease, the patient is doing extremely well eight years later, having never experienced another episode. I have chosen to discuss transient global amnesia and the related disorders for three reasons. First, this is a surprisingly common problem that often presents to primary care physicians and yet about which little is known. Second, study of the amnesic syndromes has helped unlock the door to understanding the anatomy and pathophysiology of memory, a subject of enormous interest. And, finally, this patient was my father.

Transient global amnesia is one of a group of amnesic syndromes that includes posttraumatic amnesia, drug-induced amnesia, Korsakoff's syndrome, and others. Although clinically separate and distinguishable, these various disorders share similar structural pathways. Our understanding of these diseases is a result of work in three fields: neuroanatomy, neuropsychology, and neurophysiology. After providing a background of the work in each of these fields, I shall discuss the individual clinical syndromes.

Neuroanatomy of Memory

Two thousand years of history passed before scientists learned that memory is formed and stored in the brain. The exploration of memory is rarely mentioned in classical studies of medical history, and until this century, it was the purview of only a handful of neuroanatomists.

Hippocrates (circa 460-377 BC), the first great physician, never explicitly discussed memory. He did, however, understand that epilepsy was a function of the brain and that damage to one side of that organ produced paralysis and convulsions on the other side of the body. Plato (427-347 BC) mentioned memory and thought it was located in the mind. Aristotle (384-322 BC) placed it in the heart. Galen (131-201 AD), the accepted medical authority for centuries, never mentioned amnesia. Given that he attended to injured gladiators and must have been witness to episodes of posttraumatic amnesia, this oversight is peculiar.[1]

After a long period during which few important discoveries were made, Gregor Reisch (1467-1525) developed the ventricular localization theory that identified memory as a specific function of the brain located in the fourth ventricle. This theory was illustrated in a famous woodcut that appeared in his encyclopedia of the sciences, the *Marginata Philosophica* (Figure 1). René Descartes (1596-1650), following up on this work, placed memory in the pineal gland. In 1664 Thomas Willis (1621-1675) published the *Cerebri Anatome*, the most complete and accurate description of the nervous system to that date. In addition to describing the cranial arteries and nerves and coining the word "neurology," he recognized that the cerebrum was the organ of thought and that memory was located in the cortical gyri. Like most scientists of the time, Willis depended more on imagination than empiricism. Nevertheless, many of his descriptions were surprisingly accurate.

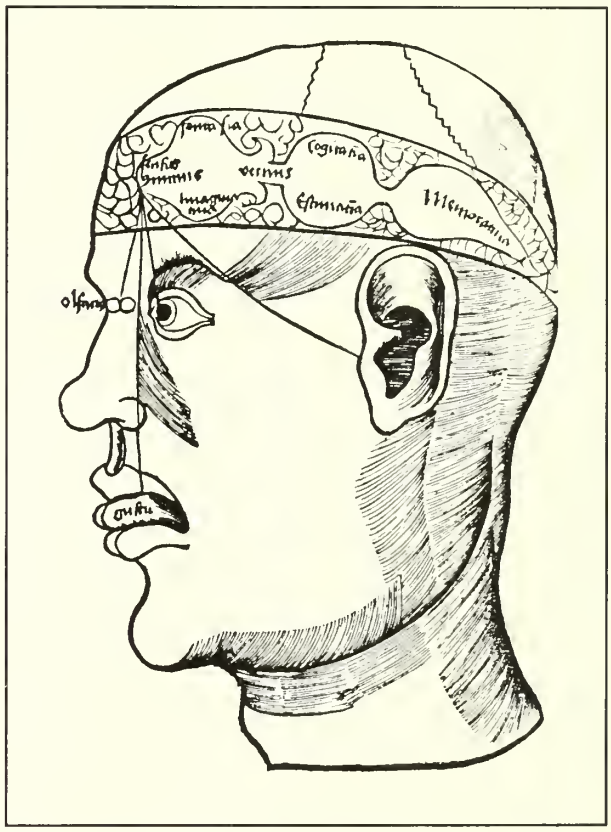

Figure 1.—This woodcut by Gregor Reisch illustrates the ventricular localization theory of psychological functions. Messages from the organs of hearing, sight, taste, and smell were thought to unite in the *sensus communis* in the forepart of the front ventricle and to produce fantasy and imagination. Thought and judgment resided in the middle ventricle. Memory is located in the posterior fourth ventricle (**Memoritiva**).

The power of modern neuroanatomic investigation of memory has been the ability to correlate functional deficits with anatomic lesions. Two famous cases provided the basis for most of the knowledge until the introduction of modern x-ray imaging techniques. The first of these was "HM," a 27-year-old man who in 1953 underwent bilateral resection of the medial temporal lobe

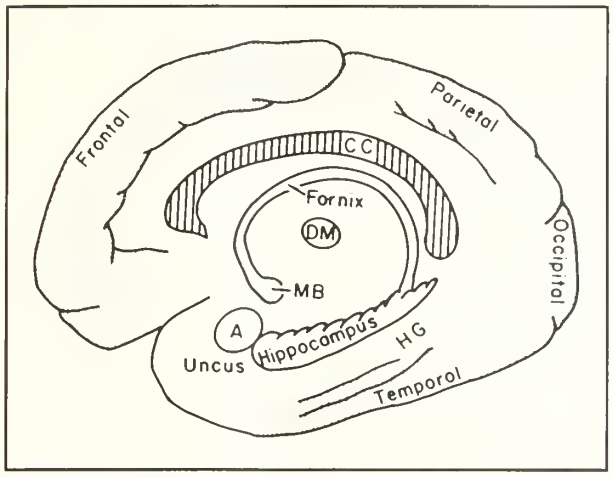

Figure 2.—The schematic represents the medial surface of one hemisphere, showing the structures most important to memory transmission. These include the hippocampus, fornix, hippocampal gyrus **(HG)**, and amygdala **(A)** in the temporal lobe, and the dorsomedial nucleus of the thalamus **(DM)** and mamillary bodies **(MB)** in the diencephalon.

region in an attempt to relieve severe and intractable epilepsy (Figure 2). In this operation both the amygdala and hippocampus were removed. Although previous unilateral temporal lobe excisions had been successful in this disease and had not caused adverse side effects, a profound amnesic state developed without any change in the patient's other intellectual abilities.[2] This syndrome is known as bitemporal amnesia and is seen in transient global amnesia, postencephalitic amnesia, and after electroconvulsive therapy.

The second case was of "NA," who became amnesic in 1960 after a penetrating brain injury from a miniature fencing foil into the region of the left dorsomedial thalamic nucleus. His syndrome has been called diencephalic amnesia, of which Korsakoff's disease is an example. Extensive study of both of these patients has led to much of our understanding of amnesia.

Magnetic resonance imaging (MRI) techniques that visualize the hippocampus in detail have recently been developed and confirm the earlier findings. A study of patients with permanent amnesia found substantial hippocampal abnormalities. A second study found patients with Korsakoff's disease to have damaged mamillary bodies and normal temporal lobes whereas patients with the characteristics of bitemporal amnesia had the opposite findings.[3,4]

Studies of monkeys have also helped to uncover the functional anatomy of the memory system.[5] By using MRI imaging and stereotactic neurosurgery, monkey preparations have been created to evaluate the loss of each component of the medial temporal lobe memory system. These studies show that the hippocampus, perirhinal cortex, and parahippocampal cortex are critically integrated and necessary for the creation of declarative memory. Contrary to previous thought, the amygdala is not part of this system and, instead, has a separate function in the control of a number of other behaviors.

Neuropsychology of Memory

Neuropsychology is a much younger science than neuroanatomy. Investigations in this field have led to the characterization of the different processes used to store and retrieve memories (Table 1). Neuropsychologists have defined two major categories of memory, declarative and procedural. Memories in the first category include facts about the world and past personal events that must be consciously retrieved to be remembered. Procedural memory, on the other hand, is what we use when learning and retaining a skill or procedure like riding a bicycle. Declarative memory can be further divided into semantic memory, the storage of "eternal" facts, principles, associations, and rules about the world (for example, that the United States is a democracy), and episodic memory, that is, information about events occurring in a specific place and time (US independence was declared in 1776).

As memory data are processed in the brain, they can be viewed as passing through several different storage "buffers" of differing capacity and duration.[6] The first of these is primary memory, also sometimes called immediate or short-term memory. It lasts half a minute and has a

TABLE 1.—*The Structure and Process of Memory*

Categories of Memory	*Description*
Categories	
Declarative	The memory subset involved in learning facts about the world and past personal events that must be consciously retrieved to be remembered
Semantic	Pertains to eternal facts, principles, associations, and rules about the world
Episodic	Pertains to events occurring in a specific time and place
Procedural	The memory subset involved in learning and retaining a skill or procedure, such as riding a bicycle
Structure	
Primary	Immediate memory (often visual); can hold up to 7 items; lasts about 30 seconds; unaffected in amnesia
Secondary	Larger, but still temporary, memory "buffer" lasting minutes to months; defective in the amnesic syndromes
Remote	Long-term memory, which includes most knowledge about the world and personal experiences
Process	
Registration	Acquisition of information; correlates with primary memory
Storage	Ability to retain information over time in an intact form
Retrieval	Ability to retrieve stored information; the final step in memory recall

capacity of about seven items (just enough for a phone number). If one is distracted during this 30-second period of memory development, the information may be lost. Secondary memory, also known as recent or short-term memory, is the second buffer. It can last from minutes to months and exhibits a much larger storage capacity than primary memory. The classic amnesic syndromes all involve defects in secondary memory. Finally, there is remote, or long-term, memory. Information is stored from months to a lifetime in this unlimited space. This area of memory includes a vast array of personal experiences and knowledge about the world.

If these terms describe what might be called a neuropsychological "anatomy" of memory, then there is also a neuropsychological "physiology" that describes the process of memory. Registration, the first step, is the encoding or acquisition of information and is the "physiologic" process that correlates with the primary memory buffer. It requires intact attention and a conscious effort. Registration is tested by asking a person to repeat a short statement immediately after it is given.

Storage, also described as retention or consolidation, is the ability to retain information over time in an intact form. This process correlates with the secondary memory buffer. Retrieval, also called decoding, is the ability to retrieve stored information and is the final step in memory recall. Like registration, retrieval requires volitional processes. Patients' ability to "store" may be difficult to separate from their ability to retrieve. Tests of storage bypass the retrieval process by the use of recognition tasks in which the information is first given alone and then after a set period of time is given again alone or alongside other items.

What is known about neuropsychology and neuroanatomy has been integrated into a "road map" for the various components of memory. Primary memory is thought to be located in the perisylvian cortex or the reticular activating system. Secondary memory, as discussed earlier, is divided between the medial temporal lobes and diencephalon, whereas remote memory (the bulk of our permanent memories) is stored in the cerebral cortex. Finally, procedural memory (as distinct from declarative memory) is thought to reside in the cerebellum.[7]

With this background, it is possible to explore amnesia, the loss of memories. Retrograde amnesia is the inability to remember events that occurred in the premorbid period. This may include information located in either secondary or remote memory. This memory loss is typically temporally graded, which means that there is a greater loss of more recent events and a better memory for more distant events. In contrast, anterograde amnesia is the inability to learn new material, a defect of secondary memory. Primary memory and registration are unaffected. Anterograde amnesia is the most pronounced and classic finding in the amnesic syndrome. In its bitemporal form (such as in patient HM), the problem is characterized by an abnormally rapid rate of forgetting. Patients with this problem can learn briefly, but quickly forget whatever it is they were taught. They are probably deficient in postencoding processes involved in the consolidation of memory. In the diencephalic type of anterograde amnesia (as in patient NA), the defect is in the initial encoding of information, with a normal ability to retain information that can be acquired. These patients have tremendous difficulty learning, but once they acquire information they retain it. An interesting current research question is whether normal forgetting reflects only a change in retrieval or is associated with a loss of information from the brain. There is considerable evidence supporting both concepts, but no final conclusion has been reached.

Neurophysiology and Neurochemistry of Memory

Neuroanatomy and neuropsychology describe the structure and organization of memory, but it will be the molecular neurosciences that eventually explain it. Most memory-related neurologic processes are conducted by one of three classes of neurotransmitter: cholinergic, adrenergic, and neuropeptide. We know that learning and memory are partially mediated by cholinergic transmission. The cholinergic route is particularly well documented in age-related memory loss. Anticholinergic agents may cause learning and memory deficits that mimic those seen in Alzheimer's disease. Furthermore, cell loss in the cholinergic-rich fibers of the nucleus basalis of Meynert as well as reductions in choline acetyltransferase activity in the septohippocampal pathway are found in brains of patients with Alzheimer's disease.[8] Yet, none of these changes are seen in patients with the amnesic syndrome.

We also know that disrupting the catecholaminergic systems disrupts memory storage, whereas agonists produce dose-dependent facilitation. Administering adrenergic stimulants does not improve memory in elderly persons, and the catecholamine systems are probably not associated with age-related memory loss. Adrenergic depletion is probably involved in the memory loss of Korsakoff's syndrome, and, as mentioned later, repletion may help.

The hypothalamic and pituitary neuropeptides may also be involved in learning, and clinically it has been shown that elderly patients given vasopressin do better on tests of attention, concentration, and memory than those given placebo. This improvement may be due to increased motivation rather than enhanced memory.

The most interesting hypothesis of memory creation is that memories are consolidated in the brain by a unique process called long-term potentiation.[9] Impulses are carried across neural synapses by calcium ions that flow through membrane channels regulated by postsynaptic *N*-methyl-D-aspartate (NMDA) and non-NMDA receptors. The non-NMDA receptors are open to calcium influx after normal, constant amplitude stimulation and mediate the usual transient depolarizations. In contrast, NMDA receptors exhibit a magnesium-mediated, voltage-dependent blockade that is only overcome by high-frequency tetanic stimulation. Once opened, the NMDA-receptor

ion channels remain open for a long period, and the dendritic ultrastructure actually changes in response. Thereafter, even after low-level stimulation, the magnitude of the postsynaptic response is increased, which accounts for "learning." Whether amnesia is due to neuron failure, chemical failure, or an interruption of this circuit is not clear.

Amnesic Syndromes

Clinically, amnesia is a loss of memory in the presence of a clear sensorium. Generally only secondary memory is affected, and primary and remote memory should remain intact. The patient's other intellectual processes should also be normal. The amnesic disorders, which include a variety of acute and chronic illnesses, all share this presentation.

Because the defect is in declarative and not procedural memory, an interesting feature common to most amnesic patients is an ability to acquire new skills but an inability to recall having previously engaged in the task. For example, an amnesic patient may be taught to solve the Tower of Hanoi puzzle, which involves moving five rings of different sizes between three pegs without ever placing a larger ring on top of a smaller one. After learning the task, these patients will repeatedly solve the puzzle perfectly but deny ever having seen it before. Table 2 summarizes the key features of the major amnesic syndromes seen in clinical practice.

Acute Global Amnesias

Posttraumatic amnesia. Perhaps the most common form of acute global amnesia is that which occurs after closed-head injuries. After recovery from traumatic unconsciousness, the last recognizable function to return is ongoing memory.

Posttraumatic amnesia is characterized by both anterograde and retrograde memory loss. The anterograde amnesia is similar to the experience in transient global amnesia, as explained later. Because of retrograde amnesia, the events that led up to a head injury cannot usually be recalled. Highly overlearned personal and demographic information is generally not lost, however. The retrograde amnesia is temporally graded, and it is rare for the period of retrograde amnesia to exceed the period of anterograde amnesia. In addition, older patients take longer to recover from posttraumatic amnesia.

There is a direct correlation between the severity of head trauma and the duration of posttraumatic amnesia. In one study, none of the 239 patients who were conscious when admitted to the hospital had amnesia for more than a day, and in 80% posttraumatic amnesia lasted less than an hour.[10] A large Glasgow collaborative head injury study demonstrated the same finding in more than 1,000 patients.[11] Coma of less than a day led to amnesia of more than a month in less than 20% of survivors, whereas after one to two weeks of coma, more than 62% had amnesia for more than a month. In addition, a relationship exists between the duration of posttraumatic amnesia and the subsequent cognitive outcome. Those with longer periods of amnesia have more permanent cognitive deficits.[12]

Closed-head injuries cause damage in three ways. *Coup contre coup* injury inflicts damage at the site of impact and directly opposite. The frontal and temporal lobes are injured by brain movement against the sharp sphenoid ridge and the rough middle fossa floor. Finally, vortex-type injuries occur in which rotary forces spread their shock waves down the brain stem.[13] Acceleration-deceleration closed-head injuries are most likely to result in memory loss. Contusions are typically found on the undersurface of the temporal lobe and probably interfere with limbic structures. Shearing forces cause diffuse damage to neural tissue, affecting particularly the white matter.

Transient global amnesia. Transient global amnesia

TABLE 2.—*The Major Amnesic Syndromes*

Syndrome	*Presentation*	*Etiology*	*Prognosis*
Posttraumatic amnesia	Acute, after closed-head injury; degree correlates with severity of injury; both anterograde and retrograde amnesia	Shearing forces of injury cause damage to limbic neural tissue	Variable; in patients without prolonged unconsciousness, usually lasts less than an hour; after coma of less than 24 hours, usually lasts less than a month
Transient global amnesia	Acute, often a precipitating event such as sex or cold water exposure; amnesia primarily anterograde with temporally graded retrograde; repetitive queries are characteristic feature	Unknown; probably due to bilateral temporal lobe ischemia from arterial spasm, atherosclerosis, or both	Excellent; nearly always resolves within 24 hours; few recurrent episodes and no notable long-term sequelae
Drug-induced amnesia	Acute onset up to 24 hours after ingestion of drug (usually benzodiazepine); otherwise similar to transient global type	Usually mediated by drugs that depress limbic neural activity; bitemporal pattern of amnesia	Excellent; resolves spontaneously
Korsakoff's syndrome	Chronic; sometimes preceded by Wernicke's encephalopathy; usually disoriented to age and place but not name; confabulation is characteristic; may have affective and psychotic features	Thiamine deficiency in the presence of alcoholism; characterized anatomically by destruction of mamillary bodies and punctate lesions of 3rd and 4th ventricles; frontal lobe may be involved	Poor; fewer than 15% of patients ever improve; thiamine supplements may help in early diagnosed cases; adrenergic agonists and serotonergic antagonists available as experimental therapy

was first introduced as a unique disorder in 1958, and in 1964 Fisher and Adams published a major monograph on the topic.[14] Over the years more than 500 cases have been reported.

This disease is more common than generally thought. A Mayo Clinic study estimated the incidence as 5.2 per 100,000 people among the general population in the Rochester, Minnesota, area.[15] In people aged 50 years and older the incidence was 23.5 per 100,000. A second prospective one-year cohort study from Finland found an annual incidence of 10 per 100,000 in the general population and 32 per 100,000 in patients older than 50.[16] In this group there was a 3:1 female-to-male predominance. The average age is 58, and the disease is uncommon in younger patients. Although the recurrence rate is 10% to 20%, patients rarely have more than three episodes.

Transient global amnesia is characterized by a severe, isolated anterograde amnesia of acute onset, without other neurologic deficits. A variable period of retrograde amnesia occurs that initially encompasses a period of days, months, or years before the attack but gradually shrinks after the attack, leaving permanent amnesia only for the events during the episode itself. Despite this temporally graded retrograde amnesia, remote memory appears to be preserved. The patients find the presence of amnesia to be extremely upsetting, and their behavior during the episode is usually marked by repetitive queries, as in the case of my father.

Attacks of transient global amnesia last 20 minutes to several hours and nearly always resolve within 24 hours. Nevertheless, subclinical memory deficits may persist for days to months. In a study of 41 patients followed up at six months and compared with a group of controls there was a small but notable verbal memory deficit present in those who had this disorder, suggesting mild permanent left-sided hippocampal-diencephalic dysfunction.[17]

Many of the affected patients mention a putative inciting event. Common themes include a cold shower or dip in the sea, sexual intercourse, an excited emotional state, and pain. In one study that actually looked at this property, 26 of 85 spells were precipitated by an event of this type.[18]

Three major explanations have been proposed for the cause of transient global amnesia, all supported, at best, by circumstantial evidence. The weakest of these views the disorder as a seizure. A second popular explanation attributes it to cerebral ischemia, calling it a transient ischemic attack of the medial temporal lobes. Finally, a new and intriguing proposal is that transient global amnesia is a form of migraine.

Epilepsy as a cause of this disorder is initially appealing for several reasons. The episodes are bizarre, bear a resemblance to partial complex seizures, and involve the temporal lobes. In addition, a few patients have been reported to have epilepsy after an episode of transient global amnesia, and one young female patient with repeated episodes of amnesia improved after treatment with carbamazepine was started.[19] Most studies, however, have failed to find electroencephalographic abnormalities consistent with seizure in patients with this disorder, except in those with known seizure disorders. Although temporal lobe epilepsy may likely present in a form similar to transient global amnesia, it is not the explanation in most patients.

Ischemia as a cause of this form of amnesia is a much more appealing hypothesis. The precipitating events of cold water dip or sexual climax can be explained as episodes of excess sympathetic activity or hyperventilation causing reduced cerebral blood flow to a stenotic vessel in an area affecting secondary memory.

In support of this explanation, we learn that as many as 70% of patients in some studies of the disorder have thrombotic risk factors.[20] In a retrospective study of 42 patients with this disorder who underwent head computed tomographic (CT) scans, 4 had lesions consistent with an acute stroke—2 in the medial part of the temporal lobe, 1 in the left thalamus, and 1 in the left lentiform nucleus.[21] This is a higher prevalence than would be expected in the general population. Furthermore, in a case-control study of 18 patients with transient global amnesia, a history of transient ischemic attacks or completed stroke was the most significant association with amnesia.[22] A cornerstone of evidence is missing, however. In virtually all large series there is no increased risk for a cerebrovascular accident after transient global amnesia.[15,20,23,24] If the disorder was, indeed, a transient ischemic attack, excess morbidity would be expected in these patients on follow-up, whereas none is found.

This leaves migraine as the most satisfactory explanation for the occurrence of transient global amnesia. The mechanism of transient ischemia is still invoked, but on the basis of spasm rather than stenosis. In a large case-control study of 114 cases of transient amnesia compared with both normal persons and controls with transient ischemia, Hodges and Wallace found no increased risk of amnesia in patients with cardiovascular risk factors. Migraine, however, was more common in patients with transient amnesia than in the control subjects.[24] In fact, all series include a high rate of migraineurs, and many patients report a headache in combination with the amnesia.[25] Cerebral blood flow studies further support this hypothesis by showing an impaired vasomotor response characteristic of migraine.[26] There are even reports of identical twins who suffer from both migraine and transient global amnesia.[27] Perhaps the most convincing evidence is the overwhelmingly benign prognosis of patients with transient amnesia. These patients are not at increased risk for subsequent stroke or transient ischemia and have no added mortality compared with unaffected controls. Although classic migraine headache is associated with an increased risk of stroke, common migraine is not.[28] Even if transient global amnesia is a form of migraine, it is not a classic migraine and should not be expected to share the same prognosis.

This is not to suggest that migraine is the sole cause of the disorder. Atherosclerosis may play a role if amnesia is a result of arterial spasm in a region of relative stenosis. Because the incidence of atherosclerosis increases with

age, this mechanism could account for the increased risk of the disorder among elderly people.

The prognosis for patients with transient amnesia is excellent. These patients should be allowed to lead normal lives, and there is no reason to restrict their driving or other activities.[29] The diagnosis can usually be made with a thorough history and physical examination, and expensive tests, such as CT or MRI scans, electroencephalograms, and angiograms are rarely needed. Patients with new neurologic findings or histories that are not consistent with the amnesic syndrome form the only exception to this rule and deserve further workup. In Hodges and Warlow's initial series of 153 patients with transient amnesia, only 114 fulfilled the criteria for transient global amnesia. Those patients who did not fulfill the criteria had a substantially worse prognosis, usually due to cerebral ischemia.[30]

Drug-induced amnesia. Benzodiazepines are the drugs that most commonly cause the amnesic syndrome.[31] Although triazolam (Halcion) is best known for this adverse effect, midazolam hydrochloride, diazepam, and lorazepam have all been reported to produce an identical syndrome. Patients typically present after taking a transoceanic flight during which they drank some alcohol and took a benzodiazepine to help them sleep on the plane. They wake up in a foreign city with the worst jet lag in their lives and no idea where they are and how they got there. The drug produces a severe but short-lived anterograde amnesia.[32]

Several other drugs can also cause the syndrome, including chloroquine, clioquinol, and alcohol. A recent report describes that scopolamine hydrobromide, which causes a transient state of anterograde amnesia and submissive behavior, is administered in Colombia, South America, for criminal purposes.[33]

These drugs probably cause problems in the encoding of memories by depressing the limbic neural activity. We know that the use of benzodiazepines decreases repetitive neural firing (which is how they stop seizures), and for this to cause a defect in memory is consistent with the long-term potentiation explanation mentioned earlier. In addition, the action of benzodiazepines may mimic that of γ-aminobutyric acid, which inhibits an excitatory loop in the hippocampus.

Chronic Global Amnesias

Korsakoff's syndrome. Korsakoff's syndrome, first described in 1889, is the most important and best understood of the chronic global amnesias. Because it is often referred to as the Wernicke-Korsakoff syndrome, it is worth clearing up the confusion created by this eponym. Wernicke's encephalopathy is the acute syndrome of thiamine deficiency characterized by mental status changes, ophthalmoplegia, and ataxia. Korsakoff's syndrome is a chronic alcoholic amnesic disorder, also due to thiamine deficiency, marked by a short- and long-term memory impairment in the absence of clouding of consciousness.

The disease can present either as Wernicke's without Korsakoff's, as Korsakoff's with no previous acute illness, or as the classic syndrome of acute encephalopathy followed by a chronic amnesic state. I shall discuss only the chronic illness.

The disease is fairly common among persons with alcoholism, and as many as 10% of patients with alcoholism and debilitating mental disease may have Korsakoff's.[34] The mean age of onset is 55, and although the disease afflicts the sexes equally, women are probably more vulnerable but have less exposure to the causal agent. Patients with Korsakoff's syndrome are alert and responsive with a normal intellectual capacity but demonstrate a profound amnesia. In addition to the expected loss of secondary memory, they have an extensive impairment of remote memory. In the past, this was thought to be due to an anterograde learning deficit that begins 10 to 20 years earlier and leads to a progressive deficit in the encoding of new memories. A good deal of evidence now supports two defects in these patients: one in retrograde memory and a second in anterograde memory.[35]

Patients are generally not oriented to age and place, but they do remember their name. They also tend to confabulate, a phenomenon sometimes seen with frontal lesions and dementia but not in transient global amnesia. Impaired attention and mood disorders may also be a problem, accounting for the term "Korsakoff's psychosis." In the acute stage, they may act euphoric, but apathy dominates the chronic phase. Hallucinations and delusions occur in as many as 20% of patients. Although neurologic signs are more characteristic of Wernicke's encephalopathy, nystagmus, peripheral neuropathy, and ataxia may persist through the chronic stage.

Korsakoff's disease is not the same as alcoholic dementia. In the latter disease there is an insidious occurrence of personality changes, abnormality of mood, and deterioration of all intellectual functions. There is no selective impairment of either intelligence or memory, and thus the two diseases can be differentiated by neuropsychological testing.

The prognosis of Korsakoff's syndrome is poor. Wernicke's encephalopathy may improve over the first two months, but established Korsakoff's syndrome is nearly always irreversible. In the most optimistic series, about 15% of patients improve over time.

The disease is characterized by small, punctate, symmetrical brain lesions along the walls and floor of the third and fourth ventricles and in the cerebellum and cerebral cortex. In most cases, the mamillary bodies are obviously involved. The frontal lobes are also usually involved, but some of this damage may be due to direct alcoholic neurotoxicity.[36]

Although thiamine deficiency is known to cause Korsakoff's syndrome, the exact mechanism of injury and its selectivity are unclear. A genetic defect in the metabolism of thiamine may be carried by some persons—perhaps preferentially expressed in women—that under normal circumstances does not result in any functional deficit. Only long-term drinkers are affected when they become thiamine deficient because of the added reductive stress incurred with alcohol consumption.

The treatment of choice is to administer thiamine as early as possible in the disease. By the time Korsakoff's is diagnosed it is usually too late for thiamine supplementation to make any difference; nevertheless, it is common practice to try a three-day course.[34] Clonidine hydrochloride, a catecholamine agonist, and methysergide maleate, a serotonin antagonist, have been given in small trials with limited success, but their use is still experimental.[37]

Other illnesses. Other diseases may rarely result in a chronic amnesic syndrome. Herpes encephalitis, caused by a virus with a predilection for the limbic system, results in a pure amnesic syndrome similar to that experienced by patient HM.[38] Other viral encephalitides, including Epstein-Barr virus encephalitis, have also been reported to cause this deficit.[39]

Electroconvulsive therapy is an iatrogenic cause of bitemporal amnesia. Although the memory loss was far more profound in the early days of this treatment when bipolar electrodes with high voltages were used, transient and sometimes long-term amnesia is still one of its major side effects.[40]

Patients with cardiorespiratory insults resulting in cerebral hypoxia are also commonly amnesic. As with trauma, memory is usually the last major cognitive function to return after a cerebral hypoxic injury.[41] The anterior thalamus and the hippocampus are the areas most consistently damaged after such injury, and the cholinergic system is particularly vulnerable to hypoxia. Acetylcholine synthesis may be impaired under even relatively mild hypoxic conditions.

An "amnesic stroke" may occur from bilateral thalamic infarction or posterior cerebral artery occlusion resulting in hippocampal damage, yet isolated amnesia due to a cerebrovascular accident is rare. Other extremely unusual but reported causes of the amnesic syndrome include recurrent hypoglycemia, brain tumor, polycythemia, and even myxomatous degeneration of the mitral valve.

Finally, amnesia is often a component of progressive neurologic diseases. Although usually accompanied by other notable cognitive findings, amnesia may be the dominant presentation in such illnesses as multiple sclerosis, Parkinson's disease, and Huntington's chorea. Of course, it is also often the presenting feature of Alzheimer's and Pick's diseases.[6]

Psychogenic Amnesia

Most of the sensational episodes of amnesia portrayed in literature and film are actually cases of psychogenic amnesia. Also known as dissociative states, these episodes are not amnesic syndromes in the classic sense but deserve discussion because of their frequent confusion with the organic illnesses.

The most common presentation of psychogenic amnesia is the fugue state, a subclass of dissociative illness also known as poriomania, dromomania, and periodic wandering. In this condition patients suddenly become totally amnesic of their past, an occurrence usually preceded by an intense emotional experience that they find overwhelming. Although patients forget their personal identity, it is unusual for them to assume a new one. They may remain like this for an indeterminate period until, typically, their memory returns spontaneously after someone provides a key to the past or until they reach a point where they feel psychologically safe. Compared with patients with the organic amnesic syndromes, these patients have total "retrograde amnesia" but intact ongoing memory. If interviewed after the administration of amobarbital (Amytal) or under hypnosis, old memories can often be elicited.

Fugue states have been described as a "tendency to avoid the awakening of emotional pain through memory."[42] Fisher studied a number of soldiers in World War II who were found wandering unprotected through the battlefields, having simply arisen mindlessly from their posts after forgetting who and where they were.[43] Through hypnosis he found that just before losing memory, they had felt powerless and out of control. The fugue state was a psychological escape from an unbearable situation. As a Freudian therapist, he interpreted the amnesia as a method of deceiving the superego by concealing the ego identity, thus preventing depression, despair, and suicidal thoughts.[44] Although this is generally a psychological phenomenon, there is some sort of fugue state in as many as 78% of patients with temporal lobe epilepsy, usually occurring in the postictal period. Therefore, temporal lobe epilepsy needs to be considered in the differential diagnosis of fugue states.

Multiple personality is the most extreme form of dissociative disorder. Patients assume a number of different personalities, whereas amnesia is often experienced by the parent personality. It is usually a result of severe and repetitive childhood trauma.[45]

Diagnosing Amnesia

The amnesic disorders are diagnosed by a good history and physical examination. Because a patient's memory deficit may be far worse than is apparent on cursory review, a complete mental status examination is requisite. For the memory tests to have validity, a patient must be able to pay attention. It is particularly important to correlate the questions asked with specific memory processes. Primary memory is tested by the digit span or the "A" test. In the digit span test, the patient is asked to immediately repeat back a sequence of six or seven numbers. In the "A" test, the examiner recites a list of letters and asks the patient to tap on the table every time the letter "A" is heard. Secondary memory is tested by asking the patient to recall three unrelated words or objects after a two- to five-minute break. Finally, asking patients about general topics, such as a list of the most recent presidents, or about their own personal history tests remote memory. Of course, far more advanced psychological tests are available, but the few tests just mentioned, in the context of a well-described history, should lead to a diagnosis in most cases.

In conclusion, when evaluating amnesia in a patient, it is most important to first determine whether the mem-

ory loss is psychogenic or organic. Usually a question as simple as, "Who are you?" can clinch that diagnosis. Whereas fugue states may be treated with amobarbital, hypnosis, and psychotherapy, the major organic amnesic syndromes still have no effective treatment. Most patients with posttraumatic, transient global, or drug-induced amnesia will get better with time, and reassurance is the key therapy. Korsakoff's syndrome and some of the other chronic disorders are open to experimental therapy, but the outlook remains grim. It is hoped that the advancing neurosciences that have provided considerable understanding of both memory and amnesia will find treatments for this and related disorders.

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Conferences and Reviews

Prognosis After Graft Replacement Operation for Abdominal Aortic Aneurysm

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We analyze findings on the long-term survival of patients undergoing elective graft replacement operations for abdominal aortic aneurysm. We review the principal surgical case series published in peer-reviewed, English-language journals over the past 15 years. Perioperative mortality was 4.0%, and 5-year survival was 69% in 16 reviewed studies encompassing 4,288 patients. Articles on late survival have largely focused on the preoperative assessment of coronary artery disease in patients who are candidates for aortic resection. The influence of other recognized risk factors, such as advanced age, hypertension, cerebrovascular disease, congestive heart failure, diabetes mellitus, and multiple aneurysms, is often not well specified in these studies. As a greater number of older patients with abdominal aortic aneurysm are seen with serious associated disease, knowledge about the expected survival of patients with surgically treated aneurysms is becoming more important to both primary care physicians and vascular surgeons when eliciting patient preferences for surgical treatment.

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In this review article we summarize the recent English-language literature on life expectancy for patients undergoing graft replacement operations for unruptured abdominal aortic aneurysms. The number of these operations performed in the United States continues to increase, from 19,000 in 1979 to more than 40,000 in 1988.[1,2] Recently published data from New York State indicate a 93% increase in the number of unruptured abdominal aortic aneurysm operations between 1982 and 1987, with a 7.2% overall hospital mortality rate reported for 1,397 unruptured aneurysm operations in 1987.[3]

Although ruptured abdominal aortic aneurysm is uncommon before age 55, the aging of the population ensures a far higher disease prevalence in the future. Because operative mortality and complications after elective aortic aneurysm procedures are substantial, physicians must be able to provide patients with accurate information about their prognosis and life expectancy to ensure they are fully informed. This review, based on peer-reviewed articles that have appeared over the past 15 years, is designed to improve physicians' ability to communicate risks and prognoses to patients with diverse medical histories.

Limitations of the Surgical Literature

Literature published before surgical treatment was used for aortic aneurysm, based largely on patients with aneurysms detected on physical examination, established that aortic aneurysms expanded rapidly and were quickly fatal. One of the last studies of aortic aneurysm mortality to be published before DuBost and colleagues pioneered graft replacement surgery in 1952 analyzed a patient cohort with a high percentage of large, symptomatic aneurysms.[4] The author reported a low (18.9%) five-year survival rate.[4] Of the 102 patients with classified causes of death, two thirds died of ruptured aneurysms, although the cause of death was unknown for a substantial percentage. Early studies of the efficacy of abdominal aortic aneurysm operations used this and other studies as comparisons for surgical outcomes.

In a frequently cited study published in 1966, Szilagyi and colleagues presented new evidence of the increase in life expectancy to be gained from elective aneurysmectomy.[5] Unoperated patients in this series had only a 19.2% cumulative five-year survival rate as compared with a 52.9% five-year survival rate for patients undergoing surgical repair. Within ten years, a third of unoperated patients died of rupture, including almost 20% of the patients with untreated "small" aneurysms thought to be less than 6.0 cm. Whereas the authors presented comparative data on risk-factor-trimmed ("standardized") groups, it should be noted that the older, sicker nonsurgical cohort used as a comparison group in this study comprised many patients deemed unfit for operation. Some patients with

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ABBREVIATIONS USED IN TEXT

CAD = coronary artery disease
QALY = quality-adjusted life years

ruptured aneurysms were included as deaths in the nonsurgical group, and patients surviving surgical treatment of ruptured aneurysms were included in late-survival calculations for the post-aneurysmectomy group.

With the exception of one population-based study by the Rochester, Minnesota, Epidemiology Project,[6] all studies of late survival for aortic aneurysm patients in the United States (and virtually all European studies) have been uncontrolled surgical case series from a single-surgeon group. Published follow-up data are generally for patients seen at high-volume academic referral centers, which usually obtain superior operative results on the basis of either surgical skill or favorable patient selection.[7,8] Much of the existing literature on late survival is also based on patients operated on during the 1970s or earlier, before the large-scale diffusion of cardiac surgery and important changes in the population prevalence of atherosclerosis. Cumulative historical results do not necessarily pertain to the older, often sicker aortic aneurysm patients treated today, many of whom may also be candidates for a staged coronary artery bypass operation.*

Epidemiology

Abdominal aortic aneurysm was the 13th leading cause of death in American men aged 55 or older in 1986.[9-11] Operative mortality rates for elective, unruptured aortic reconstruction range between 2% and 6% in academic referral centers[12-14] and 10% and 14% for low-volume surgeons and hospitals.[8] Many patients with ruptured aneurysms die before they can be admitted to the hospital; operative mortality rates for patients with ruptured aneurysms remain at historical standards of about 30% to 60% in most series over the past two decades.[15]

A dramatic increase in the incidence of aortoiliac aneurysmal disease has occurred recently. While some of the increase in detected cases of aortic aneurysm may be due to improved imaging modalities and screening efforts, the fact that more cases of both symptomatic and asymptomatic disease are being detected indicates a greater disease prevalence.[16,17] The increased incidence of aneurysmal disease may be inversely related to declining early mortality from heart disease and stroke, as aortic aneurysms in patients with cerebrovascular and coronary artery disease may develop later in life. The course of postoperative aneurysmal disease, related to either residual aneurysms not resected or aneurysms in multiple aortic segments, is also proving to be an important late survival risk factor.[18] One study reported finding new aneurysms in 11.1% of operated patients within ten years.[19]

Estimates of the current prevalence of aneurysmal disease have generally been derived from selected screening and autopsy studies. Approximately three quarters of patients with abdominal aortic aneurysms are asymptomatic when diagnosed; estimates of disease prevalence range as high as 5% of the US population older than 60.[20] Disease incidence peaks among men aged 65 to 74.[21] Although surgical referral center studies universally have far higher proportions of men with aortic aneurysms, the Rochester Epidemiology Project found a 2:1 ratio of male to female patients.[16] A recent British community screening study found a 6% prevalence rate for men older than 65.[21] A targeted ultrasound screening study conducted at a Department of Veterans Affairs medical center found a 9% prevalence rate for abdominal aortic aneurysm in male veterans aged 60 to 75 years with hypertension or heart disease.[22]

Expansion Rates

Although blood flow is a pulsatile phenomenon, the risk of aneurysm rupture is directly related to aneurysm diameter by Laplace's law. Much of the literature on the surgical selection for abdominal aortic aneurysm has therefore focused on aneurysm expansion rates and the corresponding risks of rupture. All follow-up studies of aortic aneurysm expansion rates are inherently compromised by the surgical selection of patients with symptomatic, acutely expanding aneurysms—who may disproportionately seek medical attention at referral centers. Referral center studies, often based on patients with small aneurysms or patients initially selected for nonoperative management, have reported highly variable expansion rates averaging about 0.4 to 0.5 cm per year.[23-25] Investigators from the Rochester Epidemiology Project, in the only population-based study of aortic aneurysm expansion rates in the United States, found that 75% of the patients observed with sequential ultrasound examinations (excluding surgically treated patients) had half that rate of expansion (0.21 cm per year). The risk of the rupture of aneurysms less than 5 cm in maximal transverse diameter was 0% in five years and only 3% within ten years; the risk of the rupture of aneurysms greater than 5 cm (based on the nonsurgically treated population) was 25% within five years.[26] Many Olmsted County patients in the Rochester study with small aneurysms, however, underwent surgical treatment and were thus lost to expansion rate follow-up measures in that study.

Although the Olmsted County findings contradict those of several previous referral center studies reporting higher risks of acute expansion and rupture for patients with small aneurysms—or patients with larger aneurysms who initially refused operation or who had higher initial surgical risk—they are virtually identical to the findings of recent Canadian, Swedish, and British studies.[27-29] Investigators have often noted the extreme individual variability of aneurysm enlargement and rupture. This variability undermines the usefulness of average or group mean measures of expansion. Recent efforts to standardize aortic dimensions to individual patients' body size, age, and sex promise to improve predictions of the risk of rupture and the appropriate timing of surgical intervention.[30]

*See also the editorial by D. A. Katz, MD, "Surgical Decision Making—The Repair of Abdominal Aortic Aneurysms," on pages 502-503 of this issue.

TABLE 1.—*Late Survival Data for Patients Undergoing Surgical Therapy for Unruptured Abdominal Aortic Aneurysm*

Source	*Institution*	*Patients, No.*	*Operative Years Studied*	*Operative Mortality Rate, %*	*5-Year Survival, %*	*Statistically Significant Late Survival Risk Factors*
Hertzer et al, 1980[31]	Cleveland Clinic, Cleveland, Ohio	49 Acute		26.5		Coronary artery disease (CAD)
		251 Elective	1969-1973	9.6	57*	
Whittemore et al, 1980[32]	Peter Brent Brigham Hospital, Boston, Mass	110	1972-1979	0.9	84	--
Crawford et al, 1981[33]	Baylor College of Medicine, Houston, Tex	131 Acute		7.6		
		729 Elective	1955-1980	4.3	63	Cardiac disease, hypertension, older age
Fielding et al, 1981[34]	Birmingham, England	72 Acute		18.1†		--
				19.4	66.9	
		222 Elective	1960-1979	6.3†		
				8.1	68.1	
Søreide et al, 1982[35]	5 Norwegian university hospitals	61 Acute	--	24.6	44.3	
		200 Elective		3.5	71	Older age
Hollier et al, 1984[36]	Mayo Clinic, Rochester, Minn	38 Acute				
		998 Elective	1970-1975	2.6	67.5*	Hypertension, previous myocardial infarction, angina, older age
Reigel et al, 1987[37]	Mayo Clinic, Rochester, Minn	499	1980-1985	2.8	74	CAD, coronary artery bypass, older age
Nachbur et al, 1987[38]	University of Berne, Berne, Switzerland	182	1978-1984	3.3	67.1	Older age, CAD, previous myocardial infarction
Hertzer et al, 1987[39]	Cleveland Clinic, Cleveland, Ohio	204	1978-1982	4.4	72	Inoperable CAD
White et al, 1988[40]	Department of Veterans Affairs Wadsworth Medical Center, Los Angeles, Calif	96	1972-1984	3.1	61	Goldman cardiac risk index score, cerebrovascular disease, renal disease, hypertension
Rohrer et al, 1988[41]	University of Massachusetts Medical Center, Worcester, Mass	100	1977-1987	6	69	--
Bernstein et al, 1988[42]	Scripps Clinic, La Jolla, Calif	123	1978-1985	0.8	72	Previous myocardial infarction
Roger et al, 1989[6]	Olmsted County, Minn	131	1971-1987	4.5	<60‡	CAD, cerebrovascular disease, older age
Johansson et al, 1990[43]	Karolinska Hospital, Stockholm, Sweden			7.5†		
		134	1981-1985	9.0	68	CAD
Vohra et al, 1990[44]	Glasgow Royal Infirmary, Glasgow, Scotland	41 Acute		24†	--	--
		153 Elective	1981-1986	8.5†	68.9	
Olsen et al, 1991[45]	Rigshospitalet, Copenhagen, Denmark; Scotland	151 Acute		17.2	70	2 or more serious associated diseases before operation
		287 Elective	1979-1988	4.8	80	
Total§		4,288		4.0	69*	

*Some patients with ruptured aneurysms are included.
†This figure represents the 30-day operative mortality rate.
‡Estimated from 49% 8-year survival.
§Excluding data from Roger et al.[6]

Late Survival

Table 1 summarizes the major surgical series published over the past 15 years, with data on the late survival of patients with unruptured abdominal aortic aneurysms.[6,31-45] When possible to determine from the published data, the mortality rates in Table 1 for primarily asymptomatic patients undergoing elective procedures are distinguished from those of symptomatic patients with acute conditions or patients undergoing urgent procedures for acute expansion. The five-year survival data are presented for patients with unruptured aneurysms only, except as noted. The Olmsted County study by Roger and associates, a community study, differs from the others and is therefore not included in the totals presented in Table 1.[6]

Of the patients in the 16 referral center studies listed in Table 1, 80% were men with an average age in the middle to late 60s. Several studies had somewhat older patients.[37,40-42] The operative mortality for elective patients in these series ranged from less than 1% to 9.6%, although definitions of early postoperative mortality differed somewhat among the studies. Excluding when possible the mortality results for patients with urgent or acute conditions and ruptured aneurysms, the cumulative operative mortality was approximately 4% and the five-year survival was about 69% for the 4,288 patients in these series. These totals are only suggestive because the series do not constitute a clinically homogeneous sample.

Life-table comparisons of the life expectancy of survivors of aneurysm resection with populations standardized by age, race, and sex are presented in the Mayo Clinic articles by Reigel and colleagues[37] and Hollier and co-workers.[36] The 1,066 Mayo Clinic survivors of aortic aneurysm repair between 1970 and 1975 had a five-year life expectancy that was 84.8% of the standardized population average and 70.2% of the ten-year population average (that is, 40.7% actually survived at ten years as compared with the population average of 58.0%). The excess mortality of the Mayo Clinic survivor cohort appears largely related to the burden of hypertension and heart

disease, with younger patients in their 50s and 60s having relatively worse survival than older patients undergoing successful repair in their 70s.

Findings from the Olmsted County population study by Roger and associates indicate a possibly substantial referral center bias in the literature, including the studies by their colleagues at the Mayo Clinic.[6] The authors present follow-up data on 131 community residents who underwent elective aneurysm repair from 1971 through 1987. Whereas operative mortality was similar to that reported in the studies in Table 1, the population-based study reported a 49% survival rate at eight years, substantially lower than the 66% late survival for an age- and sex-matched Minnesota population. Patients with evidence of uncorrected coronary artery disease at the time of aortic aneurysm resection, a third of the sample, had only a 34% survival rate at eight years.

Although the 53 Mayo Clinic patients with ruptured aneurysms who survived their operation had worse late survival,[36] most other series indicate few late survival differences among surviving patients with ruptured, unruptured, and urgently operated aneurysms after successful aortic reconstruction. The series reported by Søreide and colleagues[35] and Vohra and co-workers[44] had much higher operative mortality (24%) for urgent procedures but little difference in long-term life expectancy after successful operations. The lack of long-term differences in life expectancy after successful operations is probably related to the high hospital mortality of the initially sicker patients who had urgent operations or actual rupture.[41,46] Olsen and co-workers report a substantially higher percentage of patients with renal failure following surgical procedures.[45]

Risk Factors

The articles identified in Table 1 present somewhat conflicting results for certain late survival risk factors. The causes of late deaths after successful aortic reconstruction were consistently found to be coronary artery disease (CAD), which was responsible for about 40% to 50% of late deaths, and malignancy and cerebrovascular disease, which combined to account for between 2% and 20% of late deaths. The risk of fatal or nonfatal stroke was 4.2% at five years for the 1,066 Mayo Clinic survivors; 11.8% of the 572 patients dying late in that series died of subsequent complications of surgical treatment or rupture of another aneurysm, 8.2% of stroke, and 8.4% of peripheral vascular disease.[36,47] Whereas diabetes mellitus has long been documented as a major risk factor for death in peripheral vascular occlusive disease, its independent role in late mortality for aneurysmal disease is less well understood because of the small sample of patients with diabetes and aortic aneurysms.[48]

Several studies have reported higher late mortality for patients with hypertension,[33,36] although others report no differences or differences that failed to reach statistical significance.[39,42] Hollier and associates report no univariate survival effects for tobacco use, renal revascularization, or time from previous myocardial infarction[36]; these late survival risk factors are not generally reported for other series. Few data exist to evaluate the late survival effects of congestive heart failure, renal disease, or pulmonary disease, which are recognized perioperative risk factors. Most of the studies are too small to permit extensive proportional hazards, other multivariate survival analyses, or separate early and late multiphase models; these statistical methods have proved to be of great value for predicting long-term prognosis for larger samples of patients with coronary bypass and with myocardial infarction.[49,50]

Coronary Artery Disease

The most substantial body of data in the literature on aortic aneurysm operations concerns risk assessment of preoperative CAD and the appropriate timing of myocardial revascularization. Although recent myocardial infarction and unstable angina are accepted surgical risk factors, more precise and predictive measures of clinically evident CAD are being developed. In a large series analyzing consecutive patients undergoing preoperative cardiac catheterization, Hertzer and colleagues at the Cleveland Clinic found that 56% of patients with abdominal aortic aneurysms and preoperative evidence of CAD had major "correctable" lesions on coronary angiography (that is, >70% stenosis of one or more coronary arteries serving unimpaired myocardium), along with 22% of those patients without previous clinical indications of CAD.[51] In a later prospective study, Hertzer and colleagues performed cardiac catheterization on all patients with aortic aneurysms, with or without clinically evident CAD.[39] "Correctable" CAD was found in 38% and 17% of patients, respectively. These findings have subsequently been replicated by others, but controversy continues over which patients benefit most from staged coronary bypass procedures.[51-53]

The rapid increase in coronary artery bypass surgery and angioplasty may have important implications for the late survival of patients with aortic aneurysms, for whom atherosclerosis remains the leading cause of death. Summarizing the experience of patients treated from 1969 to 1973 at the Cleveland Clinic, Hertzer and co-workers found that 39% of these patients who survived the operation but died within five years died of CAD.[31] Also reflecting earlier results, Crawford and associates reported 5-, 10-, and 15-year survival rates of 54%, 34%, and 17%, respectively, for patients with previous evidence of CAD, a statistically significant difference from patients without associated disease and from patients with associated disease other than CAD.[33] Reigel and associates reported that 70% of all deaths for patients with aortic aneurysms who were operated on in their 50s or 60s were due to CAD.[37] Hollier and colleagues found a 58% five-year survival rate for patients with both hypertension and CAD, as opposed to a 74.8% five-year survival for patients without evidence of either[36]; the combination of two or more chronic diseases was also related to significantly shorter survival in the Danish series reported by Olsen and co-workers.[45] White and associates found that the long-term mortality of 96 Department of Veterans Affairs

patients older than 60 was considerably lower in the higher classifications of the cardiac risk index developed by Goldman and colleagues to predict general operative mortality.[40,54] The five-year survival rate for patients in Goldman index classifications of 1, 2, and 3/4 combined were 79%, 53%, and 41%, respectively. Although the patient sample analyzed by White and associates was too small to permit clear presentation of multivariate risks, the combination of any three factors among Goldman class 2—hypertension, peripheral vascular disease, pulmonary disease, diabetes mellitus, and large aneurysm size—predicted significantly shortened survival.[40] The study by Vohra and co-workers was one of the few in which a previous myocardial infarction had no effect on the five-year survival of patients with abdominal aortic aneurysm after successful elective resection.[44]

Findings of high operative and late mortality caused by CAD have led to various recommendations for coronary bypass graft operations for patients with aortic aneurysms and angiographic evidence of "correctable" lesions.[55,56] Currently, all candidates for aortic aneurysm resection are recommended to undergo screening for possibly operable CAD, including some form of stress electrocardiography with or without thallium imaging, followed by coronary angiography when appropriate.

Whereas some data support the highly beneficial effect of successful coronary bypass grafting for patients with abdominal aortic aneurysms, the improved survival of patients undergoing the procedures, including operative mortality for the procedures themselves, are somewhat less conclusive.[57,58] Hertzer and colleagues reported a 4.0% overall death rate for 120 staged coronary bypass and aortic aneurysm operations and found that the number of late cardiac deaths (within seven years) in this group was only slightly higher than the cardiac mortality rate for patients with normal coronaries or mild to moderate CAD.[39] The long-term survival of all patients with abdominal aortic aneurysms and "correctable" CAD in that series, including coronary bypass-related deaths, was 75%. This rate was comparable to the survival of patients with "trivial" coronary disease and far exceeded the 29% late survival for patients with aortic aneurysms who were found to have severe, inoperable CAD. Both Reigel and associates and Hollier and colleagues found no statistically significant protective effect on late survival for coronary bypass grafting in the relatively small subsamples of patients with aortic aneurysms and bypass procedures they analyzed.[36,37] Although the selection bias for coronary bypass influences these findings, Bernstein and co-workers report a five-year survival rate of 51% for patients with "uncorrected" CAD (presumably including patients with aortic aneurysms who were unfit for coronary bypass) versus 100% survival for patients with CAD and a previous successful bypass procedure.[42]

Age

The effects of advanced age are confounded by surgical selection; the selection of relatively healthier older patients may thus explain why older age has not universally been associated with significantly higher late mortality. The pattern of results by patient age, which varies widely among the series in Table 1, is clearly affected by both the historical period and various aspects of referral center selection bias.[59] In the earliest results presented in Table 1, Crawford and co-workers reported that age at the time of operation was the single most important predictor of long-term survival.[33] In that series, patients in the youngest quartile (younger than 60) had 5-, 10-, and 15-year survival rates of 71%, 53%, and 24%; patients in the oldest quartile (older than 71) had survival rates of 43%, 13%, and 11% ($P < .01$). These findings about the risk of advanced age were reproduced in the studies by Nachbur and colleagues[38] and Søreide and associates.[35] Treiman and co-workers reported an 8.6% mortality rate, a 19% postoperative complication rate, and 14% survival after five years for elective aneurysmectomy in patients 80 and older.[60] On the other hand, Bernstein and associates present optimistic findings, with a 67% five-year survival rate for patients aged 70 to 79 years and a 66% late survival rate for 20 patients older than 80.[42] Using comparisons based on age- and sex-matched populations over four decades of life, however, Reigel and colleagues report relatively higher late mortality rates for patients in their 50s (70% survival) and 60s (78% survival).[37] Interestingly, the authors indicate that the poorer comparative survival for younger patients in their 50s was unrelated to the presence of uncorrected CAD.

Conclusion

In a recent article on the expected benefit of early surgical treatment versus watchful waiting for patients with small (3- to 5-cm) aneurysms, Katz and co-workers found a 4.8% improvement in quality-adjusted life years (QALYs) for early aneurysmectomy in their baseline scenario.[61] This baseline case was for a 60-year-old man with an asymptomatic 4-cm aneurysm, an annual risk of rupture of 3.3%, and an elective operative mortality rate of 4.6%. The expected benefit of early surgical intervention (11.1 QALYs versus 10.5 QALYs in the baseline case) was obviously highly sensitive to other estimates of expansion and rupture rates and to the age of the patient. Estimates of excess late mortality due to aneurysms were applied equally to both groups in the simulation, in which 7% of the baseline cohort assigned to watchful waiting died of rupture and 70% ultimately underwent either urgent repair or elective aneurysmectomy when their aneurysms reached 5 cm (with a corresponding increase in operative mortality and postoperative complications and morbidity). Existing data did not permit differentiation of risks for patients with different chronic diseases.

The numerous ambiguities and assumptions underlying this decision model highlight the current complexities of prescriptive surgical selection decisions for patients with abdominal aortic aneurysms. An aging population and rapid improvements in diagnostic imaging techniques are likely to produce even more frequent dilemmas, such as whether to operate on the oldest old patients with small aneurysms. Over the past two decades, documented im-

provements in operative technique and postoperative care have resulted in a dramatically reduced hospital mortality rate after aortic aneurysm operations in many centers.[13,32,33,42] In part as a result of the impressive results reported for elective surgical treatment, the indications for aggressive management of aneurysmal disease have been expanding continuously. As surgical mortality has declined, at least in the published series, a number of influential surgeons have called for immediate resective treatment of all patients fit for operation with small aneurysms larger than 4 cm.[13,62] A general consensus currently exists among surgeons that patients with asymptomatic aneurysms greater than 5 to 6 cm are at high risk of preventable rupture and death and are thus candidates for immediate resective treatment, whereas patients with aneurysms smaller than 4 cm can be safely observed with sequential measurements. Unfortunately, a growing proportion of asymptomatic patients probably fall in between or have substantial chronic diseases that notably increase the operative risk of aneurysmectomy.[63]

Each patient with an aortic aneurysm must weigh the risk of rupture in the future against the significant risk of early operative mortality, combined with the fairly important risk of severe postoperative complications such as renal failure, graft infection, thrombosis, and false aneurysm formation.[19,64-66] Given the existing uncertainty about the timing of surgical treatment, particularly for the increasing population of elderly patients with substantial coexisting disease, better knowledge of patients' long-term prognosis following surgery is needed. Within the most common ranges of detected aneurysms, such information is critical to surgeons' estimates of which patients can be observed for any given interval with sequential ultrasound measurement (and control of hypertension and heart disease), which patients would benefit the most from immediate elective aneurysmectomy, and which comorbid conditions would merit deferring the operation. Better information on long-term survival is also important for patients having to balance the risk of operative death against possible gains in life expectancy. Research now being done on the appropriateness of abdominal aortic aneurysm operations should be designed to increase the information available about the interaction of late survival risk factors.

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Epitomes

Important Advances in Clinical Medicine

Orthopedics

The Council on Scientific Affairs of the California Medical Association presents the following inventory of items of progress in orthopedics. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome, and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, researchers, and scholars to stay abreast of these items of progress in orthopedics that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Orthopedics of the California Medical Association, and the summaries were prepared under its direction.

Reprint requests to Division of Scientific and Educational Activities,
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Painful Snapping Hip in Young Adults

YOUNG ADULTS with hip pain whose radiographs are normal may have one of three snapping-hip syndromes that can be treated with gratifying results. These syndromes should be differentiated from a painless deep "pop" that occurs with normal hip motion and has no clinical importance. The snapping-hip syndromes occur most often in the age group 15 through 40 years and are slightly more common in women.

The most common cause of a snapping hip is the iliotibial band snapping over the greater trochanter. This lateral snapping may be associated with trochanteric bursitis or with increased varus of the hip. It is a common cause of hip pain in ballet dancers. It may occur as a complication of total hip replacement or following an operation involving the iliotibial band at the knee.

Affected patients often say that they can "dislocate their hip." The snapping of the tendon over the greater trochanter can often be shown voluntarily by patients while standing or lying on their side. Passive internal and external rotation of the abducted limb in the side-lying position usually demonstrates the snapping. The snapping can be eliminated by walking with the limb externally rotated.

When symptomatic, this condition should be treated by stretching the iliotibial band, administering oral nonsteroidal anti-inflammatory medication, administering steroids locally, and expectant management. Surgical lengthening of the iliotibial band is occasionally indicated if symptoms are unrelieved by nonoperative management.

Another cause of a snapping hip is the psoas tendon snapping over the iliopectineal eminence of the pelvic brim as it proceeds to its insertion on the lesser trochanter. Provocative activities include walking, running, and various sports. It may occur after a hip operation that distorts normal anatomy.

Patients report a painful anterior snapping sensation. Snapping occurs with voluntary motion of the hip and usually during extension of the flexed hip at about 30 degrees of flexion. It is decreased by internal and increased by external rotation of the hip. Tenderness is associated with the snapping, just distal to the antero-superior spine and medial to the sartorius muscle.

Contrast agents can be administered along the psoas tendon to allow demonstration of the snapping tendon ("psoasgram"). Voluntary movement of the limb under fluoroscopy will allow the tendon to be viewed as it moves suddenly, coinciding with the painful snap.

As with snapping of the iliotibial band, this condition should be treated by stretching the psoas tendon and giving oral nonsteroidal anti-inflammatory medications. If symptoms are persistent, surgical lengthening of the psoas tendon may be indicated.

Snapping of the hip may also be caused by injuries of the acetabular labrum, the triangular fibrocartilaginous structure that circles the acetabulum. Labral tears occur in young patients with acetabular dysplasia or other hip disease and in young adults following twisting and flexing activities. The painful pop or snap is most often anterior, but may be posterior, and is often accompanied by a sudden weakness of the leg. The results of the physical examination are often normal, but the painful click can sometimes be demonstrated by maximum flexion or extension.

Intra-articular administration of analgesics to the hip will relieve the pain and assist in establishing the diagnosis. A computed tomographic arthrogram is the most cost-effective study in patients with persistent symptoms unrelieved by conservative management, but it will not always show a lesion of the labrum.

Arthrotomy and excision or reattachment of the torn

labrum are occasionally indicated in patients with persistent symptoms that have not responded to expectant and symptomatic management.

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Meniscal Repair

ONCE THOUGHT to be relatively unimportant, healthy functioning menisci are now known to be essential in preventing degenerative changes in the knee. The menisci decrease stress on the articular cartilage by increasing joint congruity, thereby enlarging the load-bearing surface of the joint. The meniscus also improves lubrication and decreases shear stress on the articular cartilage.

Meniscal tears with subsequent meniscectomy have been shown to lead to degenerative arthritis in the knee. Because of the importance of the meniscus in protecting the joint, attempts are now made to repair it and preserve its function whenever possible.

The meniscal tears most suitable for repair are peripheral tears in the more vascular portion of the meniscus. More central tears, degenerative tears, and radial tears, because of the relative avascularity, are not suitable for repair.

An arthroscopic technique is usually used for meniscal repair. The peripheral side of the tear and adjacent synovium are debrided to promote a vascular response and improve healing. Special instruments have been developed to allow suturing during arthroscopy. Small posterior extracapsular incisions and the placement of protective retractors are required to prevent unintentional injury to the posterior neurovascular structures.

The healing rate after meniscal repair, documented by second-look arthroscopy, is from 70% to 90%. Follow-up magnetic resonance imaging may show persistent signal changes in repaired menisci and has not been reliable in determining if a meniscus has healed after repair. Tears in the more vascular peripheral portion of the meniscus are more likely to heal. Meniscal repairs in unstable knees are less likely to heal due to the increased stress on the repair. Ligament reconstruction at the time of meniscal repair is generally recommended in unstable knees.

Postoperative treatment and rehabilitation required after meniscal repair are evolving and are somewhat controversial. Most surgeons feel that some period of restricted activity (six weeks on crutches, no sports for four to six months) is desirable to prevent excessive stress on the healing meniscus. But patients usually return to full activity within three to four weeks after a partial meniscectomy. In a young athlete, this may mean the difference between missing a few games and missing an entire season. Although meniscal repair is thought to be superior to partial meniscectomy in preventing degenerative arthritis, the procedure is too new for long-term follow-up data to be available. Current indications for meniscal repair include peripheral tears associated with ligamentous injury and isolated peripheral tears in a patient willing to comply with the postoperative restrictions. Contraindications include small peripheral tears less than 1 cm in length, as well as degenerative and radial tears.

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Male Adolescent Idiopathic Scoliosis

ALTHOUGH SEVERAL STUDIES of the natural history of patients with idiopathic scoliosis have been reported, little is known about male adolescents with scoliosis. About 20% of cases of idiopathic scoliosis occur in boys. As boys are also undergoing school screening and therefore being referred for evaluation, it is helpful to physicians to know the risk of progression for a given curve in a male patient.

In the largest study of boys with idiopathic scoliosis, 32% had a curve increase by 10 degrees or more. Several factors related to curve progression were no different in male than in female patients. The curves most likely to progress were in younger boys with immature skeletons. Children who presented with larger curves were also more likely to worsen. Boys presenting with scoliosis measuring 30 degrees or more showed a tendency toward curve progression regardless of age.

The major difference between female and male adolescent idiopathic scoliosis is that curve progression stops in girls when they reach skeletal maturity. Girls with idiopathic scoliosis stabilize after reaching Risser stage 4 (a radiographic measure of skeletal maturity wherein the iliac apophysis is fully ossified but not fused). Boys with Risser stage 4 may continue to have curve progression. This is related to their prolonged phase of vertebral growth that persists after early adolescence.

The treatment of scoliosis in boys is similar to that in girls. A careful neurologic assessment should be done to look for other causes of the scoliosis, such as neuromuscular disease. Bracing is prescribed for progressive curves and curves presenting at 25 to 30 degrees or more. Compliance with brace wear is poor in adolescent boys. Weaning from the brace should be delayed in boys until all growth has ceased, which is usually later than the radiographic appearance of maturity.

Surgical spinal fusion is indicated for patients with curves of 50 degrees or greater. Conventional surgical techniques are equally effective. In a series of 210 male adolescents with idiopathic scoliosis, fusion became necessary in 21%.

The peak age at which boys present for the evaluation of idiopathic scoliosis is 13, about two years later than girls with scoliosis. This is appropriate because skeletal development in adolescent boys is delayed compared with girls of the same age and because scoliosis in boys can develop later and progress longer.

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Physical Treatment of Soft Tissue Injuries

SOFT TISSUE INJURIES, such as strains of ligaments and muscle attachments, are often difficult to evaluate. Other than fleeting tenderness, there are few objective findings. If the injury is insufficient to cause subluxation or dislocation, physical examination, x-ray films, and even magnetic resonance imaging may not offer definitive information. Extensive physical therapy is often undertaken to reduce pain. Progress is often measured by subjective statements of pain relief. Excessive treatment, especially of injuries sustained in the workplace, has been documented. To what extent are the costs of therapy justified?

The word "injury" can be placed in quotes because it is often not clear whether the structural incompetence being treated is on the basis of progressive overload from cumulative trauma, or of a single traumatic event during an unguarded moment. Nonetheless, the rate of repair and the potential for spontaneous healing are often difficult to project when a patient is initially evaluated.

All information suggests that spontaneous healing of a non-joint-threatening soft tissue injury should be complete within five or six weeks. If not complete at that time, current evidence from sports medicine and basic studies of animals suggests that structured exercise programs are necessary to guide repair. The benefits of joint mobilization and passive treatment after six weeks or so are limited. The functional deficits created by the injury must be repaired by guided exercise programs. These principles apply to the whole array of sprains and strains that occur to all joints with cumulative or sudden overload. If the continuity of supporting ligaments and tendons has not been broken, healing is assisted by guided progressive exercises, not rest. Early passive care, such as hot packs, massage, and electrical stimulation, supports rest treatment.

If the care of soft tissue "injuries" is to be as justified as that for other medical diagnoses, the deficit must be documented through the measure of function, and measurable amounts of therapeutic exercise must be provided to guide the healing process. An assessment of the patient-client-worker's attitude must be part of the rehabilitation process. This is often accomplished by noting the patient's compliance with a measured exercise program.

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Surgical Management of Spinal Metastases

PROGRESS IN ONCOLOGY and radiation therapy, coupled with an earlier diagnosis, has led to long-term survival of patients. Patients should therefore be afforded a high degree of comfort and quality of life during their treatment. The most common malignant tumors to metastasize to the capillary beds within the large cancellous bone mass of the vertebral column include those of breast, lung, lymphatic system, prostate, kidney, gastrointestinal tract, thyroid, and others, including those that are indeterminate. Depending on the location and behavior of the spinal metastases, pain, mechanical instability, or neurologic compromise may ensue.

Metastatic cancer to bone does not itself cause either pain or neurologic compromise. Pain occurs with the loss of osseous strength. Neurologic compromise arises from ischemia due to pressure on the spinal cord or nerve roots by tumor encroachment. Surgical therapy can help manage symptomatic spinal metastatic disease.

When one or more vertebral bodies are weakened by tumor replacement, deformation (fracture) may occur. Frequently radiotherapy or chemotherapy will control tumor growth and permit bone reconstitution. Persistent pain is an indicator of instability. Restoring stability through spinal reconstruction will frequently restore comfort and the quality of life.

Even when more than one vertebra has metastases, the location of the instability can be determined by clinical assessment and radiographs. Computed tomography or magnetic resonance imaging further defines involvement. When the pedicle is the primary site of involvement and the bony trabeculae are spared, posterior stabilization, supplementing irradiation or chemotherapy, restores stability. When the vertebral body trabecular structure has been largely supplanted by tumor, anterior stabilization with allograft or other spacer is indicated. Where feasible, radiotherapy should precede surgical therapy because graft-induced osteogenesis is inhibited by postoperative irradiation. Spine implants should be designed with sufficient stability to function for the rest of the patient's life

without bony arthrodesis. Such instrumentation should be segmental, with a combination of hooks, wires, and screws used at several levels to distribute forces among normal and abnormal vertebrae. It is prudent to extend the fusion additional levels in anticipation of metastases progressing to other vertebrae. Stabilization must be imparted to those parts of the vertebrae where there is significant bone replacement, whether anterior, posterior, or both.

Metastatic tumor expansion into the spinal canal from pedicle and body may cause encroachment against the cord (cranial to L-1) or spinal nerve roots (caudal to T-10). Vertebral body collapse may cause further impingement by retropulsed bone or disc material (neither of which responds to radiation therapy). Hematogenous infection of spinal tumor may precipitate neurologic deterioration. Pain need not be associated with the development of full or lesser degrees of sensory loss or paralysis. Although paraplegia is not necessarily irreversible, surgical intervention is most effective when the preoperative neurologic deficit is minimal.

Survival after the onset of paralysis is often less than three months. If paralysis is partial or progressive, urgent surgical decompression and stabilization are often necessary. If paralysis is complete, however, particularly if the patient is free of pain, it may be prudent to accept it because the patient's life span may be less than the time required for neurologic recovery.

The metastatic lesion may be decompressed by vertebral corpectomy either posterolaterally by a transpedicular approach or anterolaterally and stabilized by anterior or posterior instrumentation. The vertebral body defect is replaced by an allograft or cement. Laminectomy alone is to be avoided.

Decision making regarding surgical therapy for intractable pain or neurologic compression should include informed deliberation by the patient and family and cooperation among the oncologist, radiotherapist, and spinal surgeon.

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Arthroscopic Shoulder Treatment—What Can and Cannot Be Done

Over the past several years, shoulder arthroscopic techniques have evolved through diagnostic capabilities to specific treatment benefits. Despite these advances, not all shoulder operations can be done arthroscopically.

Tears of the glenoid labrum are best diagnosed arthroscopically. Those not associated with instability, free flaps, or the bucket-handled type, can be easily resected arthroscopically. These represent a small percentage of labral tears. Labral tears associated with instability of the glenohumeral joint are best diagnosed arthroscopically, but reconstruction for these tears is generally accomplished by traditional open methods.

The management of rotator cuff disease has benefited from arthroscopic techniques. Partial tears of the rotator cuff, whether above on the subacromial bursal side or below on the articular side, are best seen with arthroscopy. Acromioplasty, removal of the anterior undersurface of the acromion, routinely done in association with rotator cuff repair or as an independent procedure for the impingement syndrome, is now readily accomplished with arthroscopic techniques. When combined with an open repair of small rotator cuff tears, the size and morbidity associated with the open part of the procedure can be minimized. Medium-sized and large rotator cuff tears are best handled with traditional open techniques for both the acromioplasty and the repair. Extremely large, unrepairable rotator cuff tears, often seen in the elderly, can be partially treated with an arthroscope. Debridement and acromioplasty are of value in these cases to reduce some of the pain component, although motion and strength are often not improved.

Degenerative arthritis of the acromioclavicular joint is frequently seen in association with rotator cuff disorders. Resection of the distal clavicle, a time-honored approach for this problem, can now be accomplished arthroscopically. When indicated, it can be done in association with an arthroscopic acromioplasty. As an isolated procedure, the traditional open approach is still acceptable.

Loose bodies in the glenohumeral joint as well as stubs of the proximal biceps tendon after spontaneous rupture can be removed arthroscopically. Recalcitrant painful calcific tendinitis of the rotator cuff can be removed by arthroscopy; this is often done in association with an arthroscopic acromioplasty. Frozen shoulder or adhesive capsulitis has not been treated using arthroscopic techniques.

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Prophylactic Antibiotics in Total Joint Arthroplasty

In the United States, more than 200,000 total joint replacements are done annually. Deep infection of a prosthesis results in substantial morbidity to patients and a financial burden to the health care system—estimated at greater than $200 million annually. The infection rate for

total hip and shoulder arthroplasties is less than 1%, 1% to 2% for total knee replacements, and 2% to 9% for total elbow arthroplasty. Risk factors associated with an increased incidence of infection include rheumatoid arthritis (especially in men), a previous joint operation, delayed wound healing, the presence of remote skin ulcers, malnutrition, obesity, systemic illness, immune impairment, and the presence of infections elsewhere in the body.

Numerous studies have shown that the single most important way to prevent infection is to use prophylactic antibiotics. Infection rates can be cut by more than 75% in patients with total joint replacements by using intravenous antibiotics. *Staphylococcus aureus* causes 25% to 60% of deep total joint infections. *Staphylococcus epidermidis* and *Streptococcus* species are also common causative organisms. Less frequently, gram-negative bacteria and more virulent enterococci and methicillin-resistant *S aureus* infect prosthetic joints. Most orthopedic surgeons use a first-generation cephalosporin such as cefazolin. In patients with cephalosporin allergies or when methicillin-resistant *S aureus* is suspected, 1 gram of vancomycin hydrochloride may be given intravenously over 30 to 60 minutes preoperatively. Prophylactic antibiotics are most effective when given within two hours before the operation and must also be administered at least five minutes before tourniquet inflation in cases of total knee and total elbow arthroplasty. Higher infection rates have been reported when antibiotics are given 2 to 24 hours before the operation or after the incision has been made. One dose of intravenous antibiotics is given preoperatively, and antibiotic therapy is then continued 24 to 48 hours postoperatively (usually until surgical drains have been removed). Antibiotic-impregnated polymethyl methacrylate, although useful in surgical revision, has not been conclusively shown to be more effective than intravenous antibiotics in primary total joint arthroplasty. Additional perioperative techniques, which have further reduced deep infections, include meticulous surgical technique, antibiotic irrigation, ultraclean air (ultraviolet light or laminar flow), and body exhaust systems for the operative team.

More controversial is the use of late antibiotic prophylaxis for invasive procedures in patients with preexisting total joint replacements. Many orthopedists follow the recommendations of the American Heart Association: amoxicillin, 3.0 grams orally an hour before the procedure, then 1.5 grams orally six hours later. In penicillin-allergic patients, erythromycin, 1.0 gram orally an hour before the procedure, followed by 500 mg orally six hours after the initial dose, may be used. Transient bacteremias do occur after dental manipulation, especially in association with bleeding or periodontal abscesses. Gastrointestinal and genitourinary procedures have been less frequently associated with deep infections around total joint replacements. As the bacteria from these areas are different from oral flora, the specific antibiotic used must be tailored to each case. There are no good studies documenting the incidence of infected total joint prostheses due to transient bacteremia. Until such studies become available, it would be wise to continue prophylactic antibiotic coverage before these procedures.

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Posterior Tibial Tendon Dysfunction

DYSFUNCTION OF THE posterior tibial tendon is a common cause of pain and disability in the hindfoot and midfoot in adults. The incidence of posterior tibial tendon rupture appears to equal or surpass that of tendon ruptures elsewhere in the foot. The causes of this disease include congenital or developmental abnormalities, such as the accessory navicular syndrome, degenerative arthritis, rheumatoid arthritis, generalized ligamentous laxity, overuse, and neurogenic syndromes.

The tibialis posterior muscle arises from the posterior interosseous membrane and the adjacent surfaces of the tibia and fibula. It inserts onto the navicular and the bottom of the midtarsus. It acts as a prime stabilizer to resist hindfoot valgus and forefoot abduction.

The loss of posterior tibial tendon function results in increased stress on the plantar ligamentous support of the longitudinal arch, and left untreated, these structures eventually fatigue, resulting in the acquired flatfoot deformity. The unopposed action of the peroneus brevis contributes to the pronated posture or lateral peritalar subluxation of the foot. Secondary changes such as varus or supination of the forefoot also result.

This condition most often occurs in women aged 40 or older. They report pain along the medial hindfoot and midfoot, weakness, and decreased ambulation tolerance, especially on stairs or hills. Occasionally a unilateral, insidious loss of the longitudinal arch is the main symptom. There is a history of trauma in about 50% of these patients, often reported as a missed step off a curb or into a hole or an eversion sprain.

The signs of injury include warmth, swelling, and tenderness along the course of the posterior tibial tendon, weakness to manual motor testing in a plantar flexion-and-inversion maneuver, and a tight heel cord. Other late signs include abnormal medial shoe wear, loss of the longitudinal arch, and callus under the subluxed, plantarflexed talus and navicular in the midpart of the foot. When these patients are examined posteriorly, there is excessive heel valgus, swelling posterior to the medial malleolus, and the "lateral too many toes" sign due to abduction of the forefoot. The most important provocative test for this is looking for heel inversion on a single-

stance heel-raise test. This is a function of the posterior tibial tendon locking the subtalar joint in an inverted position, thus allowing the gastrocnemius-soleus complex to plantar flex the forefoot.

The weight-bearing anteroposterior projection demonstrates an increased talocalcaneal angle and a lateral subluxation of the navicular on the head of the talus. The weight-bearing lateral projection shows a loss of the parallel axis of the talus and first metatarsal, demonstrating the flattening of the longitudinal arch. Magnetic resonance imaging is useful in unclear cases in assessing tendon sheath inflammation and posterior tibial tendon rupture.

Nonoperative measures such as nonsteroidal anti-inflammatory medication, longitudinal arch support, and casting are helpful in early stages of the disease when the tendon remains functional and no deformity is found. When these measures fail, surgical intervention needs to be considered before deformity appears. Early soft tissue procedures, such as tenosynovectomy and augmentation of posterior tendon function with the flexor digitorum longus tendon, are helpful. Once deformity has developed, however, flexor digitorum longus transfer and other soft tissue procedures will not correct the deformity. Once deformity or arthritis is observed, a bony procedure, such as talonavicular, subtalar, double (talonavicular or calcaneocuboid), or triple arthrodesis, is usually required.

This condition may be overlooked by many practitioners who are not familiar with it. Early detection and conservative management may preclude long-term deformity and extensive surgical reconstruction.

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Alerts, Notices, and Case Reports

Factitious Cushing's Disease

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CUSHING'S SYNDROME occurs frequently in patients who ingest large doses of corticosteroids long term. These patients are usually easy to identify because most are aware that they are taking corticosteroids. For the small percentage of patients unaware that they are using corticosteroid-containing creams or pills, close questioning usually reveals this fact. Occasionally, however, patients will conceal the fact that they are ingesting corticosteroids, causing their physician to embark on a long and fruitless search for an endogenous cause of Cushing's syndrome.

In contrast to factitious hypoglycemia caused by insulin administration or the ingestion of oral hypoglycemic agents,[1-3] reports of factitious Cushing's disease are rare.[4-6] We report two cases of factitious Cushing's syndrome, one caused by the ingestion of prednisolone and the other by the ingestion of prednisone. In both cases, the diagnosis of factitious Cushing's syndrome was confirmed by high-pressure liquid chromatography (HPLC) performed on urine specimens.

Reports of Cases

Case 1

The patient, a 46-year-old woman, noted progressive weakness, weight gain, leg pain, and a leg ulcer for a year before presentation. Her medical and family histories were unremarkable. She said she had not ingested any prescription or over-the-counter medications, illegal drugs, or alcohol, and she did not smoke. The patient had recently divorced and was living and working in a veterinarian's office.

On admission, her blood pressure was 196/110 mm of mercury in both arms with a pulse of 140 beats per minute and no orthostatic changes. She was obese, ruddy-faced, balding, and hirsute with a flat affect. She had central obesity with supraclavicular and dorsal fat pads present. Purple striae were noted on her breasts and abdomen. The external genitalia were normal. Erythematous papules were present in the inframammary and inguinal areas. Her thighs were deeply mottled (livedo reticularis) with a 1.5- by 1.5- by 1-cm ulcer on the left thigh. The patient walked with a pronounced limp; the neurologic examination otherwise showed no abnormalities.

Laboratory tests revealed fasting hyperglycemia with a glucose value of 13.9 mmol per liter (normal, < 7.8) and a mildly elevated leukocyte count (1.21×10^9 per liter; normal, $< 1 \times 10^9$). The rest of the routine laboratory test results, including electrolyte values, were normal. X-ray films revealed multiple vertebral compression fractures and fractures of the inferior and superior right pubic ramus.

Endocrinologic testing revealed a persistently low AM cortisol level (27.6 to 69 nmol per liter; normal, 138 to 690). The level of urinary free cortisol measured by direct radioimmunoassay was not elevated (83 to 110 nmol per day; normal, 55 to 248), and computed tomography of the adrenal and pituitary glands was normal. Because of persistently suppressed endogenous cortisol production, a diagnosis of exogenous corticosteroid use was considered. The patient repeatedly denied ingesting steroid-containing compounds or using steroid-containing creams. Urine from a 24-hour collection was analyzed by high-pressure liquid chromatography (HPLC).

Case 2

The patient, a 23-year-old woman, noted weakness, progressive weight gain, the onset of hypertension, and menometrorrhagia with resultant anemia in the year before presentation. The symptoms appeared to commence after she started taking oral contraceptives and did not remit after they were stopped. Her medical history included an appendectomy with a normal appendix and asthma (not steroid dependent). Her family history included hyperthyroidism and diabetes mellitus. The patient did not smoke, drink, or use illegal drugs; her only medication was iron sulfate. She was unmarried, worked as a part-time cashier and student, and lived with her brother.

On physical examination, she was obese and hirsute and had cushingoid facies. She appeared to be unconcerned about her illness. Her blood pressure ranged from 120/80 to 142/98 mm of mercury without orthostatic changes; her pulse ranged from 88 to 110 beats per minute, and her temperature was normal. Supraclavicular fat pads and a buffalo hump were present. Purple striae were noted on the back, abdomen, and hips. The external genitalia were normal.

Laboratory test results, including electrolytes and blood glucose, and a complete blood count, were normal except for mild anemia (hemoglobin level, 116 grams per liter; normal, 120 to 160).

Endocrinologic testing by direct radioimmunoassay, performed on an adequate 24-hour urine collection, re-

(Anderson PW, Galmarini M, Vagnucci A, Horton R: Factitious Cushing's disease. West J Med 1993; 159:487-489)

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vealed urinary free cortisol levels to be suppressed (< 39 nmol per day [14 μg per day]). Plasma cortisol levels were normal (221 nmol per liter). Computed tomography of the chest and abdomen were normal. The patient repeatedly denied taking corticosteroids in any form. Urine from a 24-hour specimen was analyzed by HPLC.

High-Pressure Liquid Chromatography Method

Cortisol in urine was measured by a highly specific technique. Cortisol and the internal standard (6-β-hydroxyprogesterone, added to correct for procedural losses) were extracted with methylene chloride. The specimen was then chromatographed with isocratic reverse-phase chromatography on a C_{18}, Waters Bondapak (10μ) 1- by 30-cm column and quantitated using UV absorbance at 254 nm. The system used was 24.5% tetrahydrofuran and 2.5% methanol and water.

Prednisone, prednisolone, dexamethasone, and cortisol were also added to the specimens to confirm that the peaks seen corresponded to the steroids in question.

The overall recovery was 90%. The sensitivity was 5 μg per liter, with intra-assay and interassay precision of 7% and 4%, respectively. Normal values were < 50 μg per day.

Results

A typical elution profile was done for urine to which exogenous prednisone, prednisolone, cortisol, and dexamethasone had been added (Figure 1), with typical retention times shown on the column.

The patient described in case 1 had no detectable cortisol in her urine by HPLC (Figure 2). A large peak was seen, however, that coeluted with prednisolone and probably represents prednisolone or its metabolite.

The patient described in case 2 also had no detectable cortisol in the urine as seen on HPLC (Figure 3). A large peak was revealed on HPLC with a retention time similar to that of prednisone, along with a smaller peak with a retention time similar to that of prednisolone.

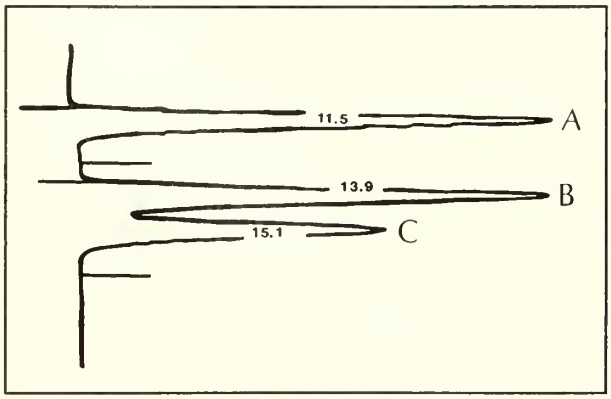

Figure 1.—A typical elution profile of extracted urine to which prednisone, prednisolone, and dexamethasone have been added, shows (A) prednisone eluting at 11.46 minutes and (B) prednisolone eluting at 13.98 minutes. Dexamethasone, eluting at 28.28 minutes, is not shown. C, The patient's endogenous cortisol is seen eluting at 15.12 minutes. The internal control, 6-β-hydroxyprogesterone, eluting at 30 minutes, is not shown.

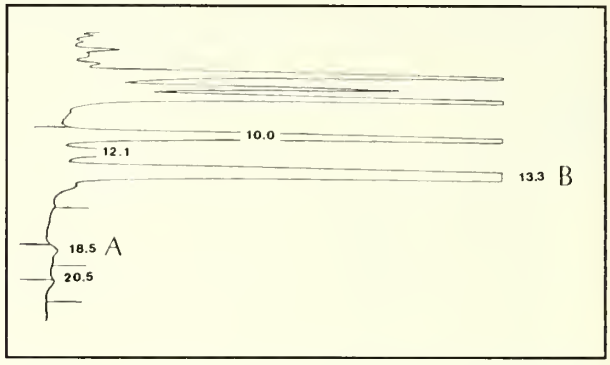

Figure 2.—An elution profile of extracted urine from patient 1 shows virtually no endogenous cortisol (A). The large peak (B) seen at 13.32 minutes is probably prednisolone.

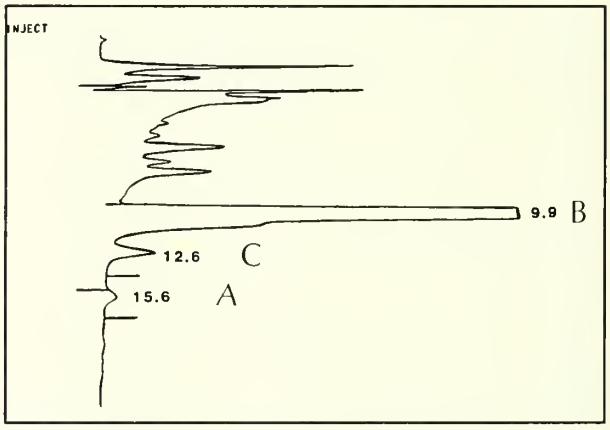

Figure 3.—An elution profile of extracted urine from patient 2 shows no endogenous cortisol (A). A large peak (B) is seen at 9.9 minutes, which is probably prednisone, and a smaller peak (C) is seen at 12.6 minutes, which coeluted with prednisolone.

Discussion

Although iatrogenic Cushing's syndrome is common, factitious Cushing's syndrome is extremely rare. Previous reports of factitious Cushing's syndrome are limited. In the case of two patients abusing hydrocortisone, in addition to the typical physical and laboratory findings of Cushing's syndrome, unusual and helpful clinical clues included extremely high plasma cortisol levels (>5,500 nmol per liter [200 μg per dl]) that varied wildly over time,[7,8] probably because the cortisol assay technique was not specific and may have been affected by cross-reaction. In the case of one patient, an infusion of corticotropin with no subsequent rise in plasma corticosterone levels was diagnostic.[8] In another case, physicians relied on the patient's confession to determine which drug was responsible for the development of Cushing's syndrome.[9]

The two patients presented here were not abusing hydrocortisone, but rather prednisone and prednisolone, and thus presented with low or normal plasma cortisol levels and low urinary free cortisol levels (measured by specific assays), indicating the suppression of endogenous corti-

sol production. High-pressure liquid chromatography has been used previously to determine the causative agent in suspicious cases of Cushing's syndrome[8] and is valuable in determining accurately which glucocorticoid has been ingested.

The reasons for the surreptitious ingestion of corticosteroids is not clear in most cases. Many persons may become psychologically dependent on the euphoric effects of glucocorticoids.[9] Alternatively, once steroid abuse has begun, it may be sustained by the development of steroid psychosis.[10] In the cases presented here, one patient feigned illness to obtain insurance benefits and thus did not suffer from a true factitious disorder, defined as a disorder that brings the patient no external gain.[11] The other patient displayed no obvious pursuit of material gains, and her motivations were unclear.

In a recent review,[12] patients with factitious disorders were found to be primarily female (> 95%), young (mean age 33 years), and employed in medically related professions (> 70%). Despite the factitious nature of their illness, they allowed extensive medical evaluations to continue. They were evasive, secretive, mistrustful, manipulative, and difficult, did not have close relationships with physicians, and generally did not seek to be admitted to a hospital. The two patients presented here were both female. One was a veterinarian's assistant and the other, although not in a medically related profession, was medically sophisticated. They allowed extensive evaluations to continue and did not seek hospital admission initially. Both patients were secretive, and physicians remarked that meaningful interaction was difficult to establish.

The treatment and prognosis of factitious disorders are complex. Confrontation, when not accompanied by accusation and abandonment, is often followed by resolution. The patient described in case 1 was confronted with the statement that her physicians knew that her disease was self-induced. The patient accepted this statement without anger but continued to deny self-induced disease. A year after her initial hospital stay, however, her signs and symptoms of Cushing's disease had vanished. The second patient also continued to deny self-induced disease, but she did not return for follow-up.

In summary, for patients who present with Cushing's syndrome and in whom factitious steroid abuse is suspected, HPLC of a urine specimen can confirm the diagnosis and identify the drug used when appropriate standards are employed.

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Isolated Pulmonary Metastases From Prostatic Adenocarcinoma

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AUTOPSY STUDIES have shown that pulmonary metastases from prostatic adenocarcinoma are common.[1,2] The pulmonary involvement, however, is typically associated with other foci of metastatic disease. Isolated pulmonary metastases occur infrequently.[3,4] We present a case of prostatic adenocarcinoma with isolated metastatic involvement of the lung found at the initial evaluation. The patient has had a complete remission following orchiectomy.

Report of a Case

The patient, a 69-year-old man with biopsy-proved adenocarcinoma of the lung, was referred for evaluation of an irregular prostate and voiding dysfunction. He complained of obstructive voiding symptoms characterized as hesitancy, decreased force of stream, and double voiding. No hematuria was reported. His medical history was unremarkable except for intermittent bleeding per rectum for six years, which the patient attributed to hemorrhoids. A physical examination showed no palpable adenopathy. There were no abdominal masses. External hemorrhoids were present, and the stool was guaiac-positive. The prostate was markedly enlarged, rock hard, and irregular, consistent with clinical stage C prostate cancer.

Hemogram and serum chemistry (SMA-20) values were normal. A prostate-specific antigen level was 117 ng per ml (normal < 4.0, Hybritech radioimmunoassay), and a prostatic acid phosphatase level was 19.8 ng per ml

(Eastham JA, Esensten ML, Wilson TG: Isolated pulmonary metastases from prostatic adenocarcinoma. West J Med 1993; 159:489-490)

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(normal < 3.0, Hybritech radioimmunoassay). A prostate biopsy done under ultrasonographic guidance showed adenocarcinoma, Gleason grade 3 plus 4. A bone scan and metastatic bone survey showed no evidence of metastatic disease. A computed tomographic (CT) scan of the abdomen and pelvis showed no adenopathy or other site of primary adenocarcinoma, but confirmed the presence of an enlarged, irregular prostate. A chest x-ray film (Figure 1) showed diffuse nodular densities throughout both lung fields; a chest CT scan confirmed these findings. Before referral, a biopsy of one of the lung nodules confirmed the presence of adenocarcinoma. An endoscopic investigation of the gastrointestinal tract to evaluate rectal bleeding revealed only hemorrhoids.

Figure 1.—A posteroanterior chest film shows multiple bilateral pulmonary nodules.

The patient was diagnosed with adenocarcinoma of the prostate with isolated pulmonary metastases and was treated with bilateral scrotal orchiectomy. Two weeks after the operation his voiding complaints had completely resolved. Serial chest x-ray films showed pronounced improvement; by eight months, all pulmonary nodularity had disappeared (Figure 2). At 12 months' follow-up, the patient remains completely asymptomatic. A bone scan continues to be normal; the prostate-specific antigen level is 1.6 ng per ml, and the prostatic acid phosphatase level is 2.0 ng per ml.

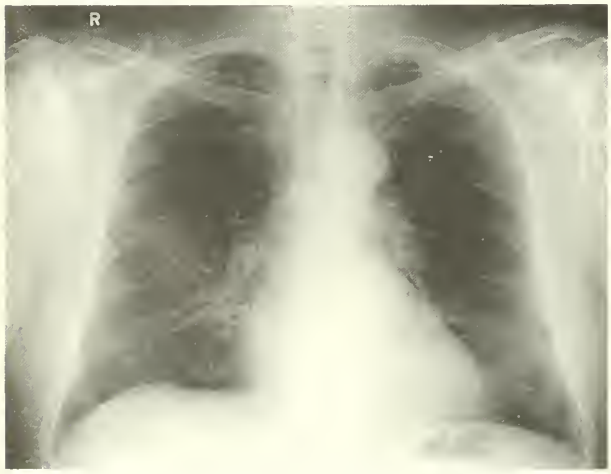

Figure 2.—A posteroanterior chest film 8 months following orchiectomy shows resolution of the pulmonary nodules.

Discussion

Pulmonary involvement in the terminal stages of prostatic cancer is not uncommon. Most large autopsy series find pulmonary metastases to be present in at least 25% of patients with disseminated disease.[1,2] Other sites of metastasis, most often skeletal, nodal, or both, are usually affected when the lung is involved. Isolated pulmonary metastases have been described, but are unusual.[3,4]

This case shows how this rare finding may present and how a dramatic remission may occur with orchiectomy. In patients with less obvious presentations, a diagnosis of adenocarcinoma of the prostate may not be considered. Gentile and associates describe a group of elderly men presenting with a clinical syndrome resembling either primary adenocarcinoma of the lung coexisting with prostate cancer or metastatic primary adenocarcinoma of the lung.[5] Each was found to have metastatic prostatic adenocarcinoma as their sole disease process. All the patients in their series responded to hormonal therapy once the correct diagnosis was made.

When metastatic disease is present but the site of origin is unknown, immunohistochemical studies may be helpful. Nadji and co-workers have used immunoperoxidase staining of prostate-specific antigen to identify tumors of prostatic epithelial origin.[6] In our patient, however, the lung biopsy specimen was inadequate for such methods. Had it been possible to do such a study, thus confirming a prostatic origin of the pulmonary lesions, a prostate biopsy with its rare but possible complications would not have been necessary.[7]

Although isolated pulmonary metastases from prostatic cancer are rare, it should be considered in the differential diagnosis in elderly men with pulmonary nodules on a chest x-ray film. Most metastatic adenocarcinomas of the lung have few treatment options available. As this case shows, however, complete clinical remission can be attained in metastatic prostate cancer with hormonal therapy. A prompt diagnosis will prevent delays in therapy and palliation in this select group of patients.

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Erythroderma Associated With Ingestion of an Herbal Product

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SERIOUS TOXIC EFFECTS from consuming herbal products are rare[1] and, until this report, have not included erythroderma. Six different ephedrine alkaloids have been isolated from Chinese ephedras.[2] Of these, ephedrine, pseudoephedrine, and norephedrine (phenylpropanolamine) are commonly used in the United States as decongestants or bronchodilators, and the other three—methylephedrine, methylpseudoephedrine, and norpseudoephedrine—are not available in the United States in pharmaceutical dosage forms.

In the case described herein, methylephedrine, ephedrine, and norephedrine are definitively identified by gas chromatography-mass spectrometry (GC-MS) in the urine of a woman with erythroderma who ingested a tablet obtained from an herbalist. Erythroderma has not previously been associated with the ephedrine group of drugs.

Report of a Case

The patient, a 28-year-old woman, was first seen in 1986 for the evaluation of a recent occurrence of generalized cutaneous exfoliation associated with adenopathy and joint pain. At the time of the evaluation, all symptoms had resolved. Since 1974, she had had six similar episodes, each of which occurred during an upper respiratory tract viral syndrome. On three occasions she had a cutaneous burning sensation that began 4 to 8 hours after she ingested various cold preparations, including Sudafed, Co-Tylenol, or Robitussin-PE,* and that would subsequently evolve over the next 12 to 14 hours into full-body erythroderma and exfoliation. In 1981 during one of these episodes, another physician noted a "scarlatiniform rash" and did a skin biopsy that revealed superficial perivascular dermatitis. Evaluation at that time included a complete blood count, chemistry panel, urinalysis, antinuclear antibody titer, throat culture, and an antistreptococcal antibody, all of which had normal values or were negative.

At the time of her first medical evaluation, there was no evidence of preexisting dermatoses, psoriasis, or cutaneous malignant lesions, and it was surmised that the patient's symptoms probably represented an idiosyncratic drug reaction to pseudoephedrine, as this was the only drug common to all of these cold preparations. The patient declined a diagnostic challenge at that time and was advised to avoid all medications containing decongestants.

Subsequently, the patient had an upper respiratory tract viral syndrome associated with nasal congestion and rhinorrhea. In an effort to obtain symptomatic relief and still avoid using decongestants, she consulted a Chinese herbalist. She was given two herbal preparations, one a tablet labeled "fruitillaria" and the other a liquid labeled "anti-virus," and was advised to take these medications four times a day. The patient was taking no other medications at that time. Eight hours after she ingested the first dose of both preparations, a cutaneous burning sensation developed with the onset of erythema over her thigh, chest, and back. The following day she was noted to have fever of 39°C and generalized erythroderma that included the plantar surfaces of her feet and the palmar surfaces of her hands. The findings of the rest of her physical examination were normal, toxic shock was ruled out, and a VDRL test was negative. No information was available from the herbalist regarding the contents of the tablet or the liquid given to the patient. Specimens of the tablet, the liquid, and the patient's urine were collected and analyzed for drug and metabolite content. Despite beginning treatment with prednisone, 40 mg, with tapering doses over the next week, the patient had a painful erythroderma. Her skin returned to normal over the next two weeks.

Materials and Methods

Chemicals

The chemicals used were trifluoroacetic acid (TFA) anhydride, ephedrine, pseudoephedrine, norephedrine, and methylephedrine (all obtained from Aldrich Chemical Company, Milwaukee, Wisconsin). Organic solvents were analytical grade.

Isolation of Drugs and Metabolites

Urine. The urine was screened for several hundred volatile and nonvolatile substances by gas chromatography and GC combined with mass spectrometry. As previously described in detail,[3] to one 5-ml aliquot of urine was added 0.5 ml of 1 mol per liter of hydrochloride or mercaptoacetic acid (9:1 volume ratio), and the specimen was heated for 60 minutes at 95°C. To this aliquot and to a second 5-ml aliquot were added 0.6 ml of 12 mol per liter of sodium hydroxide, 2 grams of sodium bicarbonate:potassium carbonate (3:2 weight ratio), and 2 ml of di-

*Sudafed (Burroughs Wellcome Company, Research Triangle Park, NC): acetaminophen, 500 mg; dextromethorpan hydrobromide, 15 mg; and pseudoephedrine hydrochloride, 30 mg. *Co-Tylenol* [now called Tylenol Cold Medication] (McNeil Consumer Products Company, Fort Washington, Pa): acetaminophen, 325 mg; chlorpheniramine maleate, 2 mg; and phenylpropanolamine hydrochloride, 12.5 mg. *Robitussin-PE* (A. H. Robins Company, Richmond, Va): guaifenesin, 100 mg; pseudoephedrine hydrochloride, 30 mg.

(Catlin DH, Sekera M, Adelman DC: Erythroderma associated with ingestion of an herbal product. West J Med 1993; 159:491-493)

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ABBREVIATIONS USED IN TEXT

GC = gas chromatography
MS = mass spectrometry
TFA = trifluoroacetic acid

ethyl ether:isopropanol (9:1 volume ratio) containing 2.5 mg per liter of phenazine as an internal standard. After vigorous mixing and centrifugation, the ether layers from the two aliquots were combined, evaporated to dryness, and derivatized by adding 100 μl of TFA anhydride and 100 μl of ethyl acetate and heating for 15 minutes at 65°C. The liquid phase was evaporated, and the derivatized products were dissolved in 0.5 ml of ethyl acetate and submitted for analysis by GC and GC-MS.

Tablet. The "fruitillaria" tablet was crushed, dissolved in 10 ml of methanol, and heated at 50°C for 10 minutes. Two milliliters of this solution was added to 8 ml of water and treated as described for the urine. In addition, 0.4 ml of the methanol solution was evaporated, derivatized directly with TFA anhydride, dried, and re-dissolved in ethyl acetate for analysis by GC-MS.

Liquid. Two milliliters of the "anti-virus" liquid was evaporated and derivatized directly with TFA anhydride. A second aliquot (1.0 ml) of this solution was added to 4 ml of water, and to this were added 0.5 ml of 5 mol per liter of potassium hydroxide, 3 grams of anhydrous sodium sulfate, and 2 ml of diethyl ether. Following mixing and centrifugation, the ether layer was analyzed by GC-MS.

Identification by GC-MS. One microliter of the derivatized mixture or extracts was injected into a Hewlett Packard 5987 GC-quadrupole MS operated in the splitless, liner scan mode (mass range, 50 to 440 atomic mass units) and controlled by a Hewlett Packard series E, 1000 computer. The GC-MS was equipped with a 17-meter, 0.2-mm ID methyl silicone column that was linked to a 0.33-μm film-thickness fused silica capillary (Hewlett Packard). The GC oven temperature program began at 110°C for one minute and then increased to 240°C at 10°C per minute. Helium was used as the carrier gas. The temperatures of the injection port, transfer line, and mass spectrometry source and analyzer were 250°C, 275°C, and 200°C, respectively. Identification of the drugs and metabolites was definitive if the retention time and mass spectrum of the unknown matched that of authentic reference standards.

Results

The tablet contained methylephedrine, pseudoephedrine, and a trace amount of ephedrine (Figure 1-A). When methylephedrine is derivatized with TFA anhydride, both the mono-trifluoroacetate and the ditrifluoroacetate derivatives are formed. No volatile substances were found in the liquid.

The urine contained methylephedrine, pseudoephedrine, ephedrine (0.1 to 0.5 μg per ml), and a trace amount of norephedrine (Figure 1-B). It also contained diphenhydramine (not shown), benzhydrol (a metabolite of diphenhydramine), and caffeine. Methylpseudoephedrine and norpseudoephedrine, optical isomers of methylephedrine and norephedrine, respectively, were not found.

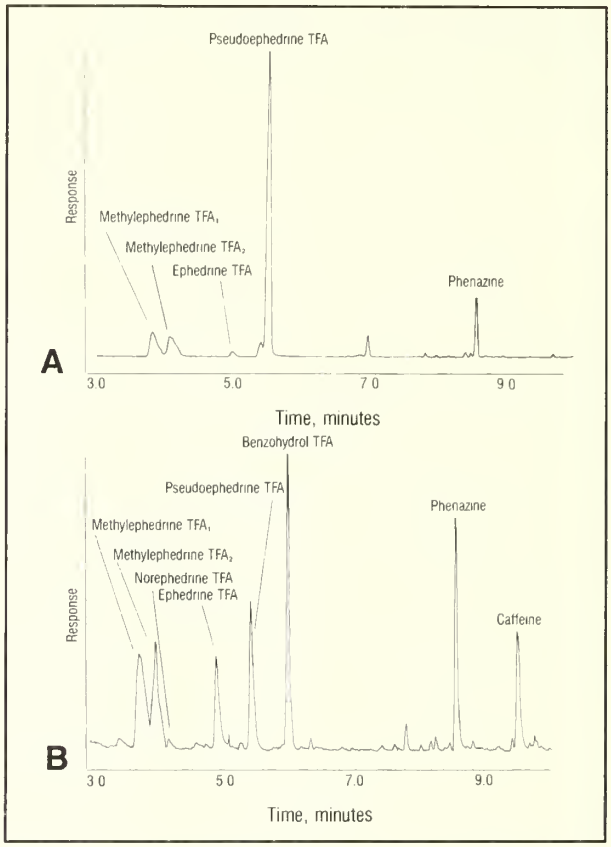

Figure 1.—Gas chromatogram was done of the urine (**A**) and an extract of the tablet (**B**). The labeled peaks are trifluoroacetate (TFA) derivatives. TFA_1 = mono-trifluoroacetate, TFA_2 = ditrifluoroacetate

Discussion

This patient experienced several episodes of cutaneous rash and exfoliation associated with a viral syndrome treated with over-the-counter decongestants. Most recently, a rash developed about eight hours after the patient ingested two herbal products prescribed by an herbalist. Erythroderma with exfoliation are most commonly caused by cutaneous diseases such as psoriasis and atopic, contact, or seborrheic dermatitides; systemic diseases such as cutaneous T-cell lymphomas, Hodgkin's and non-Hodgkin's lymphomas, and rarely some solid tumors; drugs; and idiopathic diseases. The patient had no evidence of these cutaneous diseases or neoplasms as primary causes of the erythroderma. She had previously had respiratory (presumably) viral syndromes that were not treated with decongestants, and erythroderma did not develop. Thus, it is unlikely that the underlying illnesses were the cause of the exfoliation.

Several medications have been associated with erythroderma, including allopurinol, penicillins, sulfonamides, phenytoin, gold, barbiturates, isoniazid, D-penicillamine, furosemide, sulfonylureas, captopril, and iodides. No

drugs or metabolites were identified in the liquid, but the tablet contained methylephedrine, pseudoephedrine, and a trace amount of ephedrine.

Because both the tablet and the urine contained methylephedrine and pseudoephedrine, the analytical data are fully consistent with the patient having taken the tablet. A myriad of other materials are used as preservatives and fillers in the formulation of the commercial and herbal medications. Although some of these compounds could potentially cause exfoliation, they are not likely to be the culprit medications in this case. The relatively high concentration of ephedrine in the urine (about 0.5 μg per ml) is likely the result of *N*-demethylation of methylephedrine because ephedrine is a known metabolite of methylephedrine in humans[4] and because the tablet contained only trace amounts of ephedrine. Norephedrine, a common ingredient in cold medications, was found in the urine but not in the tablet. In this case, the most likely origin of the norephedrine is *N*-demethylation of ephedrine, pseudoephedrine, or both.[4] Unreported self-administration of norephedrine cannot be completely excluded, although this is unlikely.

Most species of Chinese ephedras contain methylephedrine, methylpseudoephedrine, ephedrine, pseudoephedrine, norephedrine, and norpseudoephedrine.[2] Together these six alkaloids, the ephedrines, account for 0.04% to 2.4% of the contents of the herb. Because the tablet ingested by this patient contained only two ephedrines, it most likely was manufactured from pharmaceutically prepared drugs rather than from the herb. Ephedrine, pseudoephedrine, and norephedrine are available in the United States in a wide variety of over-the-counter cold remedies. A tablet dosage form of methylephedrine is available in Japan, Austria, and Switzerland but not in the United States. In Japan, methylephedrine is abused as a stimulant.[5] The pharmacology of methylephedrine is similar to that of ephedrine.[6]

To our knowledge, this case establishes, for the first time, a strong association between ephedrines and erythroderma. Gas chromatography-mass spectrometry was useful because of its ability to discriminate between and unambiguously identify closely related chemical compounds present in urine in low concentrations. In this patient the clinical history and the analytical finding are consistent with erythroderma induced by one or more of the ephedrines (methylephedrine, ephedrine, pseudoephedrine, and norephedrine). Both pseudoephedrine and norephedrine (as a metabolite of pseudoephedrine) could be common to each episode the patient experienced. Moreover, this case further points to the potentially serious hazards to patients with adverse reactions to medications of obtaining herbal medicaments from "alternative health care" professionals and homeopathists in which the chemical natures of the contents are unknown to both patient and provider.

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Special Series

Anatomy of Health Care Reform Proposals

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The current proliferation of proposals for health care reform makes it difficult to sort out the differences among plans and the likely outcome of different approaches to reform. The current health care system has two basic features. The first, enrollment and eligibility functions, includes how people get into the system and gain coverage for health care services. We describe 4 models, ranging from an individual, voluntary approach to a universal, tax-based model. The second, the provision of health care, includes how physician services are organized, how they are paid for, what mechanisms are in place for quality assurance, and the degree of organization and oversight of the health care system. We describe 7 models of the organization component, including the current fee-for-service system with no national health budget, managed care, salaried providers under a budget, and managed competition with and without a national health budget. These 2 components provide the building blocks for health care plans, presented as a matrix. We also evaluate several reform proposals by how they combine these 2 elements.

(Soffel D, Luft HS: Anatomy of health care reform proposals. West J Med 1993; 159:494-500)

In the first article in this series, Lee and co-workers discussed the problems confronting the health care system.[1] Two important dimensions of the problem were described: rising health care costs, and the large number of people who are uninsured. In response to these problems, a myriad of solutions are being proposed. Last year more than 40 bills were before the 102nd Congress addressing the issues of the uninsured and health care cost containment. President Clinton has made health care reform one of his major policy initiatives. In addition, reform proposals have recently been enacted in Oregon, Washington, Minnesota, Vermont, and Florida, and proposals for reform have been introduced in many other states throughout the country. A review in *The Journal of the American Medical Association* summarizes 41 proposals, including those of major presidential candidates in the 1992 election, those introduced before Congress, and proposals developed by national organizations involved in the health care debate.[3]

The proposals reflect a wide variety of approaches, from incremental to revolutionary change in the health care system. The proliferation of proposals, many with strongly ideologic presentations, makes it difficult to sort out the differences among plans and the likely outcome of different approaches. Our goal is to describe two basic features of the health care system and the way in which plans for reform address these components. These dimensions are enrollment and eligibility, as well as the organization of the system for providing health care. Various approaches addressing these two components can be brought together in different ways, depending on the philosophy and goals of a plan for reform. In some cases, a plan will address these issues directly; in others, the approach must be inferred.

A health care system must address the enrollment function—the way people get into the system and gain coverage for health care services. This includes how people are brought together in risk pools—through employment, geographical residence, age or some other demographic characteristic, or disability. Can people choose whether or not to participate? Is eligibility tied to premiums paid by employers, premiums paid by individuals, or through some tax-based mechanism?

A health care system reform must also address the organization of the health care delivery system itself. Included here are questions of how physician services are provided—in solo practice, group practice, or some more organized setting—and how such services are paid for—through a fee-for-service mechanism, capitation, or some salaried arrangement. This dimension also includes methods for assessing and ensuring quality of care and the role, if any, of health plans or other programs in providing consumers with information to make educated choices. This dimension also includes the degree of organization and oversight of the health care system at the national or regional level.

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ABBREVIATIONS USED IN TEXT

HIPC = health insurance purchasing cooperative
HMO = health maintenance organization
PNHP = Physicians for a National Health Program

These two dimensions provide the building blocks for the construction of almost any health care plan. Various options along these dimensions can be brought together in a variety of ways, based on the ideology and vision of the designers of the plan. We outline different configurations for each of the two dimensions. In the final section of the article, we look at ways these two dimensions may be put together and provide examples of actual health plans and where they fit in this matrix.

Enrollment and Eligibility

Under the dimension of enrollment, eligibility, and the mechanisms by which payment is made into the system, we outline four major models, arrayed in Table 1. In the first model, each person or family is responsible for obtaining their own health insurance. Employment-based coverage is not required in this model; rather, employers could offer a voucher or preset amount to be used for obtaining health insurance. Alternatively, funds used for health insurance benefits could be added to wages. For low-income persons, the government may provide a refundable tax credit to be used for purchasing health insurance. Persons would then obtain whatever type of health insurance they preferred, using their voucher, tax credit, and their own money. Under a variation of this plan, obtaining at least a basic health insurance package would be a mandatory, legally enforceable responsibility.[4] The Bush Administration proposed a voucher-tax credit plan, but left the decision to obtain coverage up to each person.[5] Financing for the system would come from a combination of sources, including vouchers provided by employers, vouchers or tax credits provided by the federal government, and individual out-of-pocket payments.

A second model for enrollment is the one currently seen in the United States, where most people obtain health insurance for themselves and their dependents through their employers. Health insurance benefits have long been a part of employee compensation in this country. This is a voluntary system on both sides; unlike auto insurance, where maintaining a "basic benefit package" of collision insurance is mandatory, health insurance is an option. Employers are not required to provide health insurance, and persons are not required to have health insurance. Many small businesses and businesses in the service sector do not provide health insurance due to its cost. An increasing number of workers fall outside the traditional full-time work relationship and have been referred to as "disposable workers" (P. T. Kilborn, "New Jobs Lack the Old Security in Time of 'Disposable Workers,'" *New York Times*, March 15, 1993, pp A1, A6). Furthermore, many people are not attached to a job, either directly or as a dependent, and fall outside this system. As health care costs increase and employers look for ways to reduce their commitments, health care benefits are being reduced (by eliminating coverage for dependents, for example). Thus, the voluntary nature of the system leaves many gaps in enrollment. Financing for this system is a patchwork of employer-provided health benefits (which are tax-subsidized), government programs, and individual out-of-pocket payments for health insurance.

A third model for enrolling people into health insurance programs also relies on employment-based coverage, but sees that as only a starting point for universal coverage. This model would mandate that all employers provide health insurance coverage, regardless of the size of the company. Such mandates could also extend coverage to part-time workers. In addition, this model includes expanded "gap" programs sponsored by the government for people who fall outside the work-based coverage system. This model builds on the current means by which people obtain health insurance and tries to fill in the holes. Again, financing for the system comes from a variety of sources, including employers, tax-financed government programs, and individual expenditures. Whereas coverage under such a system would be universal, the choices of health plans may vary from employer to employer.

Finally, health insurance coverage can be provided through a universal, tax-based system, thereby severing the connection between employment and health insurance. All Americans would be covered under a single, comprehensive program. It could, however, allow op-

TABLE 1.—*Enrollment and Eligibility Options*

Individual, voluntary	Persons select their health insurance coverage directly; health benefits are not offered by employers; may receive a voucher from an employer or from the government for the purchasing of health insurance; whether to obtain health insurance, how much, and what type of coverage are choices left to each person and family
Employment-based, voluntary	Health insurance most commonly received as a benefit of employment; employers choose whether to provide coverage; employees can choose whether to be insured, to what extent, and for what types of services
Employment-based, mandatory, with expanded "gap" programs	Health insurance remains employment-based; all employers are required to provide a basic level of coverage to all employees and their dependents; government-sponsored insurance programs are available to all who do not receive employment-based coverage
Tax-based	The connection between employment and health insurance is broken; insurance is universal, available to all without regard to employment status; health coverage is financed through a tax mechanism

tional supplementary insurance in addition to the basic program provided by the national system, for services not covered therein. Financing for the universal program could come through some combination of taxes, including payroll taxes, income tax, and sales tax (frequently a "sin tax" on cigarettes or alcohol is mentioned).

Health Care System

The health care system dimension of providing health care describes the way in which providers (both physicians and hospitals and other institutional professionals) are paid and organized to provide care. The role of managed care and other more organized systems is included in this dimension. An increasingly important aspect of providing health care is the way quality assurance is managed and the types of information about both quality and cost that will be available to consumers. Finally, the question of whether a national budget for health is determined by the government, and whether such a global budget is in fact a cap or simply a target, is included in this dimension.

Seven models describe different configurations of the system dimension. These range from a national health care service through the current health care system to the sort of managed competition being proposed by President Clinton. The models are organized in two categories, those that have a fixed, national budget (or expenditure target), and those that do not. The highlights of each model are described in Table 2.

The first set of models eschews global budgets or expenditure targets or limits. These models attempt to limit the growth in health care spending through various cost-containment strategies, including more actively managed care, practice guidelines and limits, a more competitive health care marketplace, reduced costs through administrative simplification and malpractice reform, rate regulation, and improved consumer decision making in selecting health care plans. Three approaches are described. (A fourth theoretical approach would include salaried providers without a national health budget. Such an approach is implausible and is not included in this discussion.)

The first of these three plans represents an incremental approach to reforming the health care delivery system, maintaining many aspects of the current system. Most providers continue to be paid on a fee-for-service basis, with most physicians in private solo or group practice. Managed care systems and other more organized systems of care may be encouraged, but are not mandated. Quality assurance and increased information to consumers are not an explicit part of this model, although a variety of approaches could be incorporated. This model represents the least amount of change from the current health care system.

The next approach, while also incremental, attempts to move the organization of providing health care more toward managed care systems. Managed systems of care such as health maintenance organizations (HMOs) are able to control health care expenditures more effectively than the traditional fee-for-service model.[6,7] Thus, many plans for reform encourage persons to move into managed care plans, mostly through price incentives. Managed care settings facilitate oversight functions of both quality and cost because they provide a centralized structure through which information can be collected and monitored.

The final model for the organization of the health care system is one of actively managed competition, the creation of the so-called Jackson Hole Group. This model re-

TABLE 2.—*Health Care System Options*

Current structure: Fee-for-service; no budget
The current approaches to physician compensation—fee-for-service, salary, and capitation—continue; costs are contained through various incremental reforms, including benefit restrictions, utilization review, and clinical micromanagement

Managed care systems; no budget
Managed care systems are encouraged; more physicians are part of organized systems of care; private fee-for-service practice, while not eliminated, becomes less competitive due to its higher cost; costs are contained through increased use of managed care systems and a variety of incremental reforms, including utilization review and clinical micromanagement

Actively managed competition; no budget
Stimulated by more organized and informed consumers and increased competition, physicians, hospitals, and insurers will form partnerships that act as integrated health care systems; each partnership decides how physician compensation will be arranged; costs are contained through increased competition; employer coalitions demand to be better informed about quality of care and incorporate some risk adjustments in premium setting for health plans

Salaried providers; national health budget
All providers are employees of the health system, receiving a salary; costs are contained through a national health budget; state and local health authorities may administer

Fee-for-service providers; national health budget
Current approaches to physician compensation—fee-for-service, salary, and capitation—continue; all providers are subject to budget caps; costs are contained through a national health budget; fees are negotiated down to stay within budget; utilization review used to constrain volume; benefit restrictions limit expenditures for certain conditions

Managed care systems; national health budget
Growth of managed care systems continues in parts of nation, but fee-for-service remains an option; overall budget is apportioned to fee-for-service or health plans; while some risk adjustment and quality assessment occur, they are relatively weak and local provider systems are rarely forced into head-to-head competition

Actively managed competition; national health budget
Physicians, hospitals, and insurers form partnerships that act as integrated health care systems; not all providers are invited to join; each partnership decides how physicians will be compensated; costs are contained through increased competition and through a national health budget; regional health authorities develop risk-adjusted payments to the various plans and provide measures of quality and consumer assessments

lies on reforming the health care sector so that a competitive market can effectively control costs and improve quality. One of the basic mechanisms of managed competition is the creation of bodies that would bring together groups of persons to be insured, establish the rules under which managed care systems (and perhaps a fee-for-service option) would compete, provide information on prices and quality, and negotiate and contract with providers and institutions. Key features of this managed competition are continually improving methods of assessing comparative quality across plans and methods to adjust payments to the health plans to reflect differences in enrollee risk.[8] These risk adjustments would force plans to compete on the basis of efficiency and quality, rather than by attempting to attract low-risk enrollees. Simultaneously, physicians, hospitals, and insurers would form partnerships that would compete for business, trying to offer the highest quality at the lowest cost. Over time, a small number of such integrated health care systems would likely dominate in a given area. Physicians would have to align with one system, although how professional services would be organized and how physicians would be paid within each partnership would be decided internally.

The second set of models utilizes the same structural components as those listed above (with the addition of a model where all providers are salaried) and adds a national budget as a mechanism for controlling costs. Within the models that use a national budget approach to cost containment, however, the rigor of those limits can vary. In some cases, the budget is truly that, and providers are forced to take the financial risk of operating in that environment. In other cases, the approach is one of targets and goals, rather than limits, and private supplementation may be allowed. Under those plans, providers are not held as accountable for expenditures that surpass the target.

The first model in this group is perhaps the most radical departure from the current US health care system. Under this model, all professional services would be provided by salaried professionals. Private fee-for-service arrangements would be eliminated. Care would be provided through organized settings such as HMOs and large group practices. The system would operate under a global, national budget. Current mechanisms for monitoring quality and cost would be inappropriate, and new methods would need to be developed.

The second model continues to allow for a variety of arrangements through which professionals are paid. Health care services would look much as they do now, with private physicians and more organized systems of care available. All physicians would, however, operate under a budget cap that would be applied at the state or regional level and translated down to the institutional level. It has been argued that such a system would necessitate that physicians collectively work to contain costs and monitor practice.[9] Global caps on spending for health care focus on the collective behavior of large groups of physicians and patients and place the responsibility for the oversight of physician behavior on their colleagues, rather than on an external utilization review agent. If such efforts are not sufficient, fees would be negotiated downward to stay within the budget.

The third model in this group relies increasingly on managed care systems, although fee-for-service arrangements do continue. The overall global budget is apportioned between managed health plans and the fee-for-service option. Managed care systems are placed at risk for containing costs, whereas fee-for-service physicians operate under a fee schedule.

The final model that operates under a budget cap uses the managed competition approach among health plans to encourage more appropriate and cost-effective care. Physicians and hospitals would form partnerships to offer a coordinated package of care, with payment arrangements left to each partnership to decide. New entities would be created in each state or region to provide cost and outcome data that would allow people to make informed choices as to which health plan to enter, coordinate the enrollment of individuals into health plans, and collect premiums and redistribute them to the plans. A national health budget, designed to add discipline to the health care market, could use both the regulation of premiums—defining some caps on the premiums that health plans are allowed to charge—and rate regulation for providers practicing under fee-for-service arrangements as means to enforce expenditure limits.

Configuring the Health Care System—Options for Reform

The two dimensions of the health care system are arrayed in a matrix, presented in Table 3. A number of current health care programs (both domestic and international) have been arrayed on the matrix, along with several proposals for health care reform. These approaches illustrate some of the many ways that the two functions of the system can come together. The way that persons are enrolled into the health care system and whether or not an overall budget exists do not proscribe the way in which the health care system is organized. These two dimensions operate independently, although some combinations are unlikely due to practical or philosophical reasons. For example, it is difficult to picture salaried professionals in systems without an explicit budget.

Providing a detailed examination of each of these programs is beyond the scope of this article. Rather, we highlight a few examples illustrative of approaches to reform and also briefly discuss two current programs (one domestic, one international) that illustrate different ways that the building blocks can come together. Furthermore, few "pure" models exist, so most of the examples offered have some features that do not fit their stylized descriptions.

Current United States Health Care System

The current health care system has no explicit budget (some exceptions to this include the Department of Veterans Affairs and some Medicaid programs). Enrollment

is mostly employment based, with 77% of American workers offered access to employer-sponsored group health insurance.[10] In addition, some government programs are targeted at specific populations based on demographic characteristics (most notably, Medicaid for low-income people and Medicare for elderly and disabled people). Enrollment in the current system is voluntary on all sides. Persons are not required to have health coverage; employers are not required to provide coverage; and insurers may reject high-risk persons for coverage, may exclude preexisting or specified conditions, such as the acquired immunodeficiency syndrome, from policies, and may have no limits on the premiums they may charge.

The current US health care system relies largely on a system of private practice physicians reimbursed on a fee-for-service basis. Managed care systems have been growing, but as of 1990 only 15% of the US population were enrolled in HMOs,[11] although HMO penetration varies substantially by geographic area. About 40% of all physicians are in solo private practice, and 75% are remunerated on a fee-for-service basis.[12]

Tax-Based, Fee-for-Service System—Physicians for a National Health Program

The proposal put forth by Physicians for a National Health Program (PNHP) is a single-payer model that restructures the enrollment and financing functions, yet retains much of the structure of the current health care delivery system.[13,14] Eligibility is automatic, with consumers becoming part of their state's risk pool by virtue of their living in that state. The program would transfer funds from all the sources that currently fund the health care system—publicly funded health programs such as Medicaid and Medicare, state and local government expenditures for health care, employer contributions through payroll taxes, and revenues from private health insurance—into the public program.

The PNHP proposal does not recommend any changes in the organization and provision of health care services. Free choice of physician and practice arrangement for patients is maintained. The proposal includes three payment options for physicians. These are fee-for-service, salaried positions in institutions receiving global budgets (hospitals, health centers, group practices), and salaried positions within group practices or HMOs receiving capitation payments. Fee-for-service practitioners would be reimbursed based on a binding fee schedule (with balance billing prohibited). Physicians working in hospitals or clinics would be employees of those institutions and would receive a salary. Health maintenance organizations and group practices that chose to be reimbursed on a per capita basis would also hire physicians on a salary basis.

Mandatory Employment-Based, Managed Competition Scenario—Enthoven and Kronick and the Jackson Hole Group

The managed competition approach was originally articulated by Enthoven and Kronick in a two-part article in 1989.[15] The plan mandates that all employers provide health insurance to all employees, contributing 80% of the cost of an average plan that meets a federal standard of benefit level. This employment-based system would be complemented by payroll taxes on part-time employees and taxes on non-poor nonemployed persons (such as early retirees),[16] so that the system becomes universal.

Under the managed competition approach, persons are brought together in groups referred to as health insurance purchasing cooperatives (HIPCs). These groups are

TABLE 3.—*Illustrative Health Care Programs and Proposals*

	No Explicit Budget				*Notional Health Budget*			
Health Care Programs	*Salaried Providers*	*Fee-for-Service Providers*	*Managed Care Systems*	*Actively Managed Competition*	*Salaried Providers*	*Fee-for-Service Providers*	*Managed Care Systems*	*Actively Managed Competition*
Individual, voluntary	--	Heritage Foundation Supplemental Medicare		--	--	Private supplemental option in British National Health Service	--	--
Employment-based, voluntary	--	Current US health care system (Bush)		--	--	--	--	--
Employment-based, mandated, with gap programs	--	Hawaii American Medical Association	Enthoven, Jackson Hole Group		--	Germany	--	--
Tax-based	--	--	--		Veterans Affairs British National Health Service Physicians for a National Health Program	Canada	Medicaid programs with managed care option (New York, California)	Garamendi

regional corporations whose function is to pool groups of people and act as purchasing agents in negotiating with health care plans. All persons enroll in the health plan of their choice through their employers or the HIPC, either of which acts as an intermediary between consumers and the health care system. The HIPCs and large employers offset the problem of biased selection by adjusting premiums paid to health plans to account for differences in health risk of the enrollees. They also preclude unfair and misleading marketing practices. The HIPC would also provide information on cost and quality to inform consumers about their health plan.

The managed competition scenario encourages the development of more organized systems of care as a more cost-efficient alternative to the current fee-for-service system. It has been argued that the more organized systems use internal oversight mechanisms that effectively maintain quality while reducing cost by changing financial incentives for physicians. They do this by monitoring practice patterns and physician outcomes and by matching the specialty and technology mix more appropriately with the need for specialized services.[16] Although this approach does not mandate any specific organizational format, it is expected that the growth of organized systems of care will lead to a diminution of the fee-for-service sector. The competition between health plans encouraged by this approach would also lead to overall cost reductions in the health sector.

Tax-Based, Managed Competition Scenario Under a National Health Budget—Garamendi Proposal

John Garamendi, the Insurance Commissioner for the State of California, has developed a proposal for health care reform for that state that incorporates many of the elements of a managed competition approach, but differs from the previous plan in two key ways. First, the plan is financed through tax mechanisms, and second, it operates under a global budget.[17] Under the plan, most Californians would obtain their coverage through one health care system, managed by a private or public partnership. (Medi-Cal recipients are not included under the current version of the plan due to joint federal-state financing and the high cost of bringing Medi-Cal benefits up to the level of the basic benefit package that would be guaranteed by the plan.)[18] Financing would be pooled, with money coming from payroll taxes (with small businesses paying a lower tax rate), a premium on wages and salaries (with low-income earners paying less), and a premium on earnings for those who are self-employed. Regional purchasing corporations would link consumer groups directly with health plans and guarantee that a minimum benefits package (defined by the state) was available to everyone in that region. The purchasing corporation would also perform the oversight functions described earlier in the actively managed competition scenario.

The Garamendi plan would further encourage California residents to enroll in managed care systems. Already almost half of Californians are enrolled in HMOs.[11] Fee-for-service arrangements, while permitted under the Garamendi plan, would probably require out-of-pocket payments by consumers to pay the difference in cost between that system and the least-expensive basic benefit package. Such financial incentives are likely to discourage extensive use of the fee-for-service option over the long run. It is also expected that competition would drive health plans to become more integrated, as such integration reduces costs.

Finally, unlike the previously described managed competition scenario, the Garamendi plan would operate under a global budget. Rather than relying on competition as the sole mechanism for cost containment, the Garamendi plan includes global budgeting as a backup system of cost control.[19] Global budgeting is achieved through capitated payments to health plans, with each health plan paid only the per capita amount equivalent to the cost of the basic benefit package. Plans may offer amenities, such as greater freedom of choice of providers, but consumers must pay for such amenities directly, "softening" the budget cap.

Voluntary, Fee-for-Service System Under a National Budget

Great Britain has operated a National Health Service since 1948. Most people in Britain receive most of their health care services through this service. The British system has always allowed a private, fee-for-service system to operate alongside the national system. Private insurance is available, obtained by persons on a voluntary nonsubsidized basis, and paid for out-of-pocket. Even physicians primarily employed by the National Health Service can provide service to private patients on a direct, fee-for-service basis by scheduling certain private clinic hours.

Tax-Based, Salaried System Under a National Health Budget

Health care is provided for American veterans through the Department of Veterans Affairs, which operates an extensive network of hospitals. Anyone who has served in the armed services is eligible to receive care through this system. Care is provided free for health care problems that are related to military service. Copayments are required for health care problems that are not service-related. The system is financed through general tax revenue and operates under an annual budget determined by Congress. Physician services are provided through salaried arrangements, either directly or through contractual relationships with medical schools or universities.

The Bottom Line

Although most people agree that the health care system needs to be reformed, underlying values and attitudes shape opinion about the best approach. Attitudes about individual rights, the role of government, incremental over revolutionary change, and the appropriate role of the medical profession shape our responses to proposals for reform. A number of examples illustrate this point. Some proposals rely on informed consumer choice to improve

competition in the health care marketplace (such as ex-President Bush's[5] and the Heritage Foundation's[4]). Others focus on consumer choice among health plans, with quality being assessed by bodies that manage the operation of the competition (such as the Garamendi plan[17] or the Jackson Hole Group's approach). Some proposals (Physicians for a National Health Program[13,14]) include an expanded role for government-run health care programs. These proposals are based on the belief that competition fragments the delivery system and generates excessive marketing and administrative costs and that the government can run high-quality, efficient programs. Many find this a dubious assumption.

The degree of egalitarianism that is desired also shapes preferences for a health care plan. Whether to allow a multitiered health care system, or to require a universal level of care without optional add-ons, is based on beliefs about the role of government and the extent to which people with more income should be allowed to demand a more responsive or otherwise superior system. These choices also reflect beliefs as to the ability of the political process to address difficult budgetary conflicts between tax rates, physicians' incomes, medical technology advances, and patient preferences. Finally, some people approach reform as if they could design the optimal system from scratch. Others are much more cognizant of the current realities and attempt only incremental changes. How such issues are approached may also depend on whether a long-term goal is being outlined or a "final offer" presented for immediate implementation.

Assessing the likely outcome of any proposal for health care reform is difficult. Uncertainty exists about the feasibility of specific approaches. Managed competition has not really been tried anywhere; fixed budgets have not been imposed on bloated systems. The accuracy of cost projections necessitates high-quality data, accurate forecasting models, and assumptions about the future (such as the degree of economic growth),[20] all of which are problematic in the current health care debate. President Clinton is proposing to move in a direction new to American health policy, and our ability to predict how things will unfold is fraught with uncertainty.

In general, it is easier to imagine how things might change with proposals that basically tinker with the existing system. Sweeping changes are more difficult to assess because the details are lacking, so the blanks in the scenario are typically filled in according to individual fears or fantasies. We have attempted to avoid including our own assessments of the various proposals, but rather to focus on highlighting some of the key dimensions of all proposals. Given both enormous uncertainties about the outcome of any health care reform proposal and differing preferences for choice, access, cost containment, and other factors, a single "best" approach is unlikely to emerge. The use of the matrix presented here allows for the separation of structural components of reform from the ideologic underpinnings and assumptions we all bring to the debate over health care reform. With a common understanding of the questions, it should be easier to have a fruitful dialogue as the debate progresses.

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Editorials

Aging and the Heart

AGING IS AN INEVITABLE biologic process characterized by a progressive reduction of the functional reserve capacity of various organs. It is best represented by a progressive decline in maximal aerobic exercise capacity ($\dot{V}O_2max$), which occurs at a rate of 10% to 11% per decade in sedentary people after about the age of 25 years.[1,2] The $\dot{V}O_2max$ is the largest amount of oxygen that a person can consume per minute during an incremental exercise test to exhaustion. It reflects the capacity of the cardiovascular system (cardiac output) to deliver oxygen to the working skeletal muscles and of the skeletal muscles to extract oxygen from the blood (arteriovenous oxygen content difference) to generate energy by oxidative phosphorylation for mechanical work (Fick equation: $\dot{V}O_2max$ = maximal cardiac output × maximal arteriovenous oxygen content difference). The age-related decline in aerobic exercise capacity is mediated by reduced cardiac output and reduced arteriovenous oxygen content difference due to impaired oxygen extraction by working skeletal muscles; aging has a greater effect on the former than on the latter. The reduced cardiac output at maximal exercise in the elderly (60 years of age and older) is the result of a lower maximal heart rate and maximal stroke volume.

There are structural and functional changes in the heart and blood vessels with advancing age, characterized by abnormal left ventricular diastolic function, resulting in impaired diastolic filling[3,4]; diminished left ventricular systolic reserve manifested by an inadequate rise in the ejection fraction during exercise[5]; decreased sensitivity to catecholamines, resulting in diminished myocardial contractility and heart rate response[6]; and increased arterial stiffness[7] leading to an increase in afterload, particularly during exercise. These changes together result in a suboptimal rise in the stroke volume and heart rate during maximal exercise that, in turn, is responsible for the decline in the $\dot{V}O_2max$ in the elderly.

Elsewhere in this issue, Michael Crawford, MD, has presented a thorough description of age-associated changes in cardiac function and structure and their clinical implications.[8] He has emphasized that the degree of impairment of the physical working capacity varies in elderly persons. This heterogeneity is the consequence of a number of factors, including the habitual level of physical activity, genetic factors, and chronic diseases commonly associated with advancing age, notably hypertension, coronary artery disease, valvular heart disease, diabetes mellitus, and other diseases, such as amyloidosis. The presence of one or more of these factors can influence the severity and manifestations of cardiac dysfunction in the elderly. For example, the age-associated left ventricular dysfunction appears to be much less striking in physically active healthy older subjects than in their sedentary peers, as evidenced by adaptations to exercise training in older subjects.[5,9,10] The improvements in left ventricular systolic[5] and diastolic function[10,11] induced by endurance exercise training are, in part, responsible for a higher aerobic work capacity seen in physically active elderly persons and can enhance their quality of life. Evidence suggests that aging per se (primary aging) can influence left ventricular systolic function. This effect is detectable almost exclusively during exercise and manifested by diminished left ventricular systolic reserve with a smaller increase in left ventricular ejection during peak exercise than in younger subjects.[5] In contrast, there is no detectable impairment of left ventricular systolic function at rest.

Although echocardiographic measures of left ventricular filling dynamics should not be equated with left ventricular relaxation, they nevertheless reflect left ventricular filling that can profoundly influence stroke volume through the Frank-Starling effect. Altered left ventricular filling dynamics (decreased E and increased A waves of the transmitral Doppler profile) are probably inconsequential in the elderly population at rest because stroke volume is maintained partly because of the compensatory increase in late diastolic filling (similar to that seen with hypertension). During exercise, however, where an increased heart rate restricts diastolic filling progressively, the enhanced late diastolic filling manifested by increased A wave velocity may not be sufficient to maintain an adequate stroke volume. Therefore, the age-associated decrease in diastolic filling along with a diminished sensitivity to catecholamines and an increased arterial stiffness can result in a lower maximal cardiac output in the elderly.

There is an inverse relation between age and coronary artery flow reserve. Older subjects tend to have diminished coronary blood flow reserve partly due to a higher resting coronary blood flow than in younger persons because of the higher cardiac work caused by higher blood pressures in the elderly.[12]

Available evidence suggests that the age-associated decline in cardiac performance is generally more striking during exercise than at rest and varies in severity depending on the presence of associated cardiovascular diseases, the level of habitual physical activity, and probably genetic factors. Older patients with underlying coronary artery disease, diabetes, or hypertension are likely to exhibit a more pronounced cardiac dysfunction in response to stress than younger patients with a similar degree of disease involvement. A sedentary life-style can contribute to the impaired cardiac performance, resulting in a decreased physical working capacity. Regularly performed endurance exercise such as walking and cycling is likely to ameliorate the age-related cardiac dysfunction, partially prevent the decline in physical working capacity, and improve the quality of life in elderly persons.

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Surgical Decision Making—The Repair of Abdominal Aortic Aneurysms

GREATER DIAGNOSTIC CAPABILITY has allowed for the more frequent, incidental detection of disease in the preclinical stages. Most abdominal aortic aneurysms are detected as incidental findings. In a population-based study of Rochester, Minnesota, residents over a 30-year period, 78% of patients with aortic aneurysms were asymptomatic at the time of diagnosis.[1] When diagnosis by physical examination and plain x-ray film was replaced with diagnosis by ultrasonography, the incidence of small aneurysms increased tenfold. The prevalence of abdominal aortic aneurysms in a recent screening study ranged from 2% (from the perspective of the clinician performing the physical examination) to 9% (from the perspective of the ultrasonographer).[2] Clearly, abdominal aortic aneurysm represents a spectrum of disease, the management of which depends on its size and the clinical context in which it is found.[3]

Because of the high mortality associated with aortic aneurysm rupture, the pressure to intervene early is great. Large aneurysms (>5 to 6 cm) have high rupture rates without therapy. For small aneurysms in the 4- to 6-cm range, patients who are managed nonoperatively may have a higher aneurysm-related mortality rate than patients who receive surgical treatment. These observational studies, which are biased by surgical selection, form the basis for the recommendation that patients with small aortic aneurysms undergo periodic surveillance ultrasonography, followed by an elective operation when a predefined size has been reached.[4,5] For small aneurysms (<4 cm), the risk of rupture is negligible.[6,7] Consequently, there appears to be consensus among experts regarding the treatment of patients with aneurysms at either end of the spectrum (>6 cm or <4 cm), but there is a lack of agreement regarding the management of aneurysms in the 4- to 6-cm range.[8] Several clinical trials have been initiated to determine whether the early repair of abdominal aortic aneurysms improves survival, but the results are not expected until 1995 at the earliest.

Clinical decision analysis is a useful tool for this type of problem and has been applied to difficult decisions involving aortic aneurysm operations. Pauker used decision analysis to examine the optimal delay before surgical therapy in the case of a 51-year-old patient with an expanding 8-cm aneurysm who also had had a recent anterior myocardial infarction.[9] The basic philosophy of decision analysis is to break a complex problem into its component parts and to attack each of those components separately (for example, how rupture risk varies as a function of aneurysm size over time or how perioperative mortality decreases as a function of time since myocardial infarction). An advantage of this approach is the explicit documentation of the reasoning process and the data base from which the decision is made.[9] Sensitivity analysis allows the investigator to determine the clinical variables on which the decision hinges—such as the probability of dying before surgical therapy if an aneurysm ruptures. Further efforts can then be focused on obtaining more precise data—or, in some cases, data unique to a particular patient—for those key variables.

In a recent analysis, we found that the decision between early elective surgical intervention and "watchful waiting" (expectant management until the aneurysm reaches a predetermined size) for patients with small aneurysms depends on four variables: perioperative mortality, the risk of rupture under "watchful waiting," age of the patient, and the size threshold at which an operation is performed (such as 5 cm).[10] Clearly, long-term survival following aortic aneurysm repair, captured primarily by age in the foregoing analysis, is important in surgical decision making.

In this issue, Feinglass and co-workers describe the epidemiology of abdominal aortic aneurysm and summarize the surgical literature regarding long-term survival following aneurysm repair.[11] Interpretation of the data cited in this review is limited by referral bias. Some unifying concepts emerge from the review, however. First, coronary artery disease (CAD), aneurysmal disease in other portions of the aorta, and stroke account for the largest proportion of deaths in survivors of aortic aneurysm surgery. Second, the long-term survival of patients with aortic aneurysms who have uncorrected, substantial CAD is consistently worse than that of patients without significant CAD. And third, the effect of age on long-term survival is obscured by surgical selection because relatively healthy older patients undergo surgical treatment. Unfortunately, no population-based studies on long-term survival following surgical therapy report in a standardized manner data on age, sex, CAD, and other serious associated diseases[12] that affect long-term survival.

Other things being equal, long-term survival is integrally related to age. Long-term survival in patients can be divided into two components: the all-cause mortality rate adjusted by age, sex, and race, and the excess annual mortality rate associated with the specific disease state of interest. The latter can be estimated from the difference between observed mortality for patients with a specific disease and the expected mortality for persons in the general population matched for age, sex, and race. For example, the life expectancy of a 5-year-old child with leukemia is primarily determined by the excess mortality associated with leukemia and, to a small extent, by the age-, sex-, and race-adjusted mortality rate for a 5-year-old child. In contrast, the overall life expectancy of an 80-year-old man following aortic aneurysm repair will be primarily determined by the adjusted mortality rate for that age and less so by the excess mortality rate associated with aneurysmal disease.

To illustrate the effect of age on surgical decision making, consider two patients, one 50 years old and the other 80 years old, who each have an asymptomatic 4-cm abdominal aortic aneurysm and average operative risk. The estimated survival benefit of early aneurysmectomy relative to "watchful waiting," for the 50-year-old patient is 0.82 quality-adjusted life years, compared with 0.13 quality-adjusted life years for the 80-year-old patient.[10] The case of prostate surgery for localized prostate cancer also illustrates this effect: The estimated benefit of total prostatectomy becomes vanishingly small as age increases.[13] In patients with asymptomatic disease, physicians must be prepared to discuss the tradeoff between the immediate risk of an operation and the small (often negligible) survival benefit of surgical therapy with their elderly patients.

Feinglass and colleagues have addressed an important component of the decision involving elective aortic aneurysm repair and have called attention to the need for more precise estimates of long-term survival following surgical therapy that incorporate relevant concurrent illnesses. In conjunction with more accurate data regarding the size-specific risk of aneurysm rupture and perioperative mortality, these data will enable physicians to provide patients information relevant to the decision of whether or not to undergo elective abdominal aortic aneurysm operations.

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Timely Reporting of AIDS Cases

To the Editor: Two recent articles described advances in the clinical diagnosis and treatment of patients with human immunodeficiency virus (HIV) disease.[1,2] Another important but less obvious role physicians play in combatting this epidemic is the timely reporting of confidential case information on the acquired immunodeficiency syndrome (AIDS) to local health departments.[3] Substantial delays often exist from AIDS diagnosis until case information is received and processed by local and state health departments. This time lag creates an artificial plateau or decline in the epidemic curve, which may lead to false conclusions about AIDS trends.

We recently developed statistical estimates of the distribution of reporting delays in California and identified variations in this distribution by region and other case characteristics.[4] Statewide, 60% of cases are reported within six months of the AIDS diagnosis, and 80% are reported within a year after diagnosis. Delays in reporting AIDS cases vary by route of HIV exposure, with the longest delays in reporting occurring among recipients of blood or blood products. Overall, reports on younger persons with AIDS have much longer delays than reports for those in older age groups.

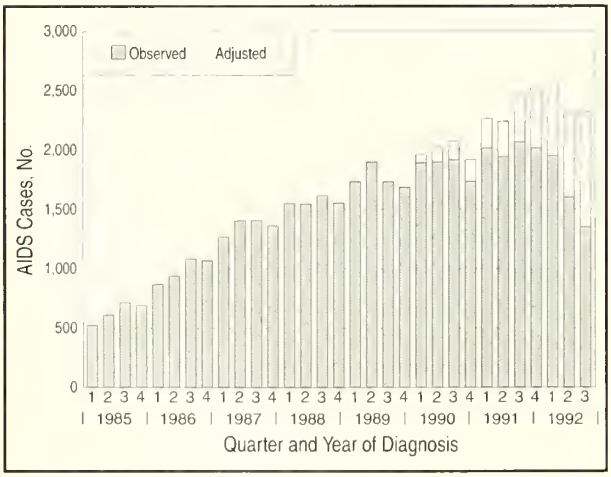

Figure 1.—Diagnosed cases of the acquired immunodeficiency syndrome (AIDS) per quarter in California, observed and adjusted for reporting delays, are shown. Cases meeting the expanded case definition effective January 1993 are not included (from the California Department of Health Services, Office of AIDS).

Based on the estimated reporting delay distributions, statistical adjustments can be made to more accurately reflect trends in the occurrence of AIDS (Figure 1). These adjusted trends provide more accurate information to assist physicians in guiding efforts to prevent the further transmission of HIV.[5] The adjusted incidence also provides more effective health planning and policy assessments through more accurate estimates of the prevalence of HIV infection and the future incidence of AIDS.

Data on AIDS occurrence are also used in the allocation of resources for HIV prevention and for the care and treatment of persons infected with HIV. For example, federal funding to California under Title I and Title II of the Ryan White CARE Act depends in part on morbidity statistics, as does the state's allocation of these funds to local consortia for care and treatment services for those infected with HIV. Because observed, not adjusted, AIDS morbidity statistics are used in these funding decisions, timely and complete reporting of AIDS cases is needed to ensure an equitable allocation of resources.

The need for improved timeliness of case reporting is heightened by the recent expansion in the AIDS case definition effective January 1, 1993.[6] This may double the number of AIDS cases reported this year.

Physicians, nurses, and other health care professionals are encouraged to work closely with local health departments to improve the timeliness and completeness of reporting cases of AIDS.

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Abnormal Mammogram After Steering Wheel Injury

To the Editor: The mammographic and clinical findings resulting from noniatrogenic trauma to the breast can be mistaken for signs of malignancy, especially because trauma often is not considered as a cause for such findings. Furthermore, patients may not initially recall the traumatic event.

We report a case of trauma to the breast resulting from a motor vehicle accident, showing a unique, diagonal mammographic pattern of calcified oil cysts resulting from a steering wheel injury.

Report of a Case

The patient, a 49-year-old woman, was seen for evaluation of a pea-sized mass felt in her left breast. A mam-

mogram done with a metallic skin marker over the mass showed multiple fat-density masses with eggshell-type calcification characteristic of fat necrosis, one of which corresponded to the palpable mass (Figure 1). The patient described a motor vehicle accident seven years before this visit in which she sustained direct trauma to her left breast from the steering wheel, resulting in extensive black-and-blue marks. The distribution of the calcified lipid cysts, which extended diagonally across the breast, was thought to correspond to the course of the steering wheel, suggesting fat necrosis from blunt trauma. The patient's x-ray films from three years before the examination showed no change. The reason why the palpable region of fat necrosis came to the patient's attention seven years after her initial injury could not be ascertained from her medical record.

Figure 1.—Craniocaudal **(top)** and mediolateral **(bottom)** mammograms show eggshell-type calcifications in a diagonal distribution across the breast resulting from blunt trauma from a steering wheel during a motor vehicle accident.

Discussion

The breast can be subject to direct trauma in a motor vehicle accident, with bruises and abrasions of the chest wall occurring in 16% of seat belt-restrained victims, as detailed in a large prospective surgical series.[1] The investigators reported that minor soft-tissue injuries sustained by restrained passengers tended to be restricted to a diagonal band over the chest corresponding to a seat-belt harness. The most common mammographic findings resulting from major breast trauma—usually surgical biopsy—are breast edema and skin thickening, architectural distortion, dystrophic calcification, mass, and changes of fat necrosis.[2,3] Fat necrosis may produce a hard mass that can be adherent to the skin or deeper structures.[4] Previous mammographic findings after seat-belt injury or motor vehicle accident have included the disruption of a silicone-gel breast implant, breast mass with or without skin thickening, dystrophic calcifications of fat necrosis, or a spiculated mass suggestive of breast cancer.[5-7] None, however, have described the diagonal mammographic pattern from the distribution of injury incurred during motor vehicle accidents. In our patient, the diagonal pattern was probably caused by blunt trauma from the steering wheel, resulting in eggshell-type calcifications suggestive of fat necrosis. We postulate that the diagonal distribution could also be produced by the harness-type restraining seat belt. In our practice we also have noted a hematoma restricted to the axillary tail from a seat-belt injury and three cases of fat necrosis or lipid cysts strictly localized to the inner breast after seat-belt or steering wheel injury.

Patients may not initially remember the traumatic event to the breast, and mammography may be the first radiographic study to suggest this history, particularly if it shows typical findings of fat necrosis. The region should be evaluated to ensure that the calcifications or mass have a typically benign appearance that would correlate with the type of injury incurred, perhaps with fine-detail mammographic views. Films should be taken with skin markers to document that palpable findings correspond to the characteristic benign fatty lobule or region of fat necrosis seen on mammography. Careful, short-term follow-up to document the stability of the clinical and radiographic findings may be substituted for biopsy when both the mammographic findings and temporal relationship of these findings are consistent with the clinical history for blunt injury to the breast after a motor vehicle accident and the suspicion for malignancy is remote.

Because wearing a restraining seat belt is now the law in many states, mammographic findings after motor vehicle accidents may not be uncommon. Recognizing the diagonal pattern described here may be helpful in distinguishing sequelae of blunt trauma. Other mammographic appearances of fat necrosis such as a spiculated mass (not

shown in our case) may mimic carcinoma, however, and only those findings pathognomonic of benign fat necrosis should be dismissed after mammographic workup.

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Complications of Do-Not-Resuscitate Orders

To the Editor: The article by Olsen and colleagues in the May 1993 issue[1] was a thought-provoking addition to the bioethics literature. The authors, however, did not mention several other community initiatives besides those in Anchorage, Alaska, and Hennepin County, Minnesota, to allow home do-not-resuscitate status (DNR). In California, both Los Angeles and Orange counties have provided for DNR orders in the home. Orange County provides special DNR wristbands to home health agency patients, with consents signed by the patient or a surrogate and the physician. These are honored by paramedics and hospital emergency physicians. Los Angeles County requires a copy of a signed DNR order instead of a wristband.

Vertically integrated managed care organizations control many aspects of health care delivery. FHP Healthcare, a federally qualified health maintenance organization, has policies in its Long Beach/Orange County Staff Model Region that provide for hospital and skilled-nursing-facility social workers to counsel and obtain consent for postdischarge DNR orders. Our ambulance department, emergency departments, skilled nursing facilities, home health and hospice agencies, and ambulatory centers have policies to honor these orders. The purpose of this set of policies is to allow our organization to honor patients' wishes in all settings.

Implementing these policies is difficult. We have created special color-coded arm bands to identify DNR patients, but few patients will wear them. Without this identification, when cardiovascular collapse occurs, health care professionals who do not know the patients will resuscitate them. Checking data bases for DNR orders, finding orders for ambulatory patients, or calling designated agents is not possible for resuscitation teams. Families should be taught to anticipate the stages of death and call the home health or hospice nurse when a patient with a DNR order collapses, rather than use an emergency medical system. Furthermore, local regulations hamper our ability to comply with patient wishes.

The local emergency medical system will not honor our company-specific wristband. Because our facilities and patients cross county lines, at times we must use both counties' systems and paperwork for the same patient. Families of these patients often use the emergency medical systems when faced with the reality of imminent death. When no wristband is in place, patients are resuscitated and taken to the nearest paramedic receiving center, away from the physicians and nurses who may know these patients or have access to their records. Our local regulations consider patients who call for an ambulance after discharge from the hospital "prehospital." The discharging physician's DNR order is not valid in that case until the first home health visit. Therefore, our own ambulances are prohibited from honoring do-not-resuscitate orders for some recently discharged patients.

Verbal DNR orders are often proscribed, and few physicians make home visits. FHP Healthcare's home health department does include close contact with physicians and physician visits to a patient's home when necessary. Still, unlike hospital DNR orders, we cannot change home DNR orders daily. Delays caused by the logistics of obtaining a home DNR order result in unwanted resuscitation.

Despite these obstacles, we must continue to develop ways to implement such policies. The acceptance of terminal illness involves grieving. Once patients or their families have understood and accepted medical limitations and have chosen a course of limited intervention, we have a duty to honor that choice. We must remove bureaucratic and logistical impediments to fulfilling that duty.

Resuscitating patients with terminal illnesses who do not wish that intervention is futile and unwanted care. We currently face an economic and political environment that may lead to reduced medical benefits. Before we limit care that is effective, or that a patient wants, we should make every effort to eliminate care that is both unwanted and ineffective.

I also urge that "state governmental agencies . . . propose comprehensive DNR legislation for prehospital settings."[1]

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* * *

To the Editor: I was pleased to read Olsen and colleagues' article regarding the need for do-not-resuscitate (DNR) orders in the home so that paramedics are not forced, because of legal mandates, to disregard a patient's autonomy.[1] Recently we admitted a 52-year-old woman with advanced metastatic breast carcinoma to our intensive care unit, intubated her, and initiated pressor agents despite her well-known and documented desire not to be resuscitated.

This patient, a member of the Hemlock Society, also had a durable medical power of attorney and had left a handwritten note saying that she wanted to die. She was found by paramedics in her home with agonal respirations. After a frenzied series of phone conversations, including some with the city attorney's office and local police departments, the paramedics were advised that they were duty-bound to try to save her life. Had they not done so, they were told, they would have been subject to prosecution for abetting a suicide.

While intubated and unconscious, she developed a tension pneumothorax and had to have a chest tube thoracotomy done. After a painful and prolonged intubation and stays at two different hospitals, she finally went home, where she died about eight weeks after this unfortunate and somewhat callous saga had begun.

Under a new state law persons in Colorado now can reject cardiopulmonary resuscitation by signing a form received from their physician. The law was intended for terminally ill patients who prefer to die at home instead of being rushed off to a hospital. Another facet of this dignified measure is to protect emergency personnel when they are faced with patients who clearly do not want treatment to prolong their agony. The State of Colorado has heeded the exhortation of these authors to establish a viable system for home DNR orders in their communities. Patient care will be truly enhanced through the widespread acceptance of this system.

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Dr Lowenstein Responds

To the Editor: We appreciate the opportunity to respond to these letters. It is encouraging to learn from Dr Mehler and Dr Harding that other states, counties, and municipalities are working to develop prehospital do-not-resuscitate (DNR) policies. Harding has outlined in detail several important barriers to implementing prehospital DNR policies—proof of patient identification, the need for patients to wear wristbands or bracelets, the ambivalence of family members who call 911, the needs that patients and family members sometimes have to change their minds, and conflicting policies and protocols that arise when different paramedic units cross county and city lines.

As Mehler mentions, since we conducted our study in Colorado, the Colorado legislature has passed legislation and the Colorado Medical Society has developed a detailed protocol to implement home DNR orders. The program is new. It is already evident, however, that implementation will face some obstacles. Physicians throughout the state must be sent educational material describing the legislation, the rationale for the program, and the means to secure at-home DNR orders for their patients. Fundamental changes in paramedic protocols must take place. Efforts must be made to coordinate home DNR orders with existing emergency department and inpatient do-not-resuscitate protocols. Citizens throughout the state must be made aware that they can request home DNR orders, that they must sign special documents, and that they can also purchase wrist bracelets that say "do not resuscitate" and that contain their name and identifying information. In addition, given the cost of the DNR bracelets—currently $27—a means must be found to assist indigent patients to purchase them. Finally, as with any new health care policy, it is essential to collect data to analyze the effect on patient care and comfort.

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The Potential Effects of Enterprise Liability

To the Editor: The term enterprise liability, unknown to most physicians until the past few months, is seen with increasing frequency in the medical and public press. The concept is not new—airline pilots and employed physicians have long been protected from liability for their errors and omissions by primary accountability of an airline or health plan.

What is new, and particularly important to physicians in private practice, is the application of "enterprise liability" to hospitals.

Hospital liability, though not yet required by any state legislature, is recommended and best described in Paul Weiler's book, *Medical Malpractice on Trial*,[1] as one of four proposals to counter the "malpractice problem." If this proposal is implemented, hospitals will be liable for negligence by medical staff members; physicians will not be legally responsible for negligent actions. The supposed deterrance factor of malpractice law will be shifted from the physician to the hospital, giving a hospital moral and economic clout to evaluate, assess, and discipline physicians to a degree far beyond current medical staff oversight.

Much that is now written of enterprise liability relates to its application to managed care entities, such as health maintenance organizations, where, in many instances,

physicians' responsibility and obligations are still being negotiated.

Physicians are correct in being apprehensive that what would seem a welcome relief from malpractice insurance costs may instead be trouble. If legislative or regulatory pressure produces hospital liability for medical staff decisions, only a fundamental change in the relationship between hospital and physician staff will permit the continuing influence of physician judgment to be a dominant factor in the appraisal and assurance of quality of care and in the evaluation, counseling, and credentialing of the medical staff.

Concerned physicians might well begin to explore the organizational possibilities that differ from the conventional governing board–administrator–medical staff arrangement. Loosely affiliated staff status may no longer be tenable when changes in law interpose a hospital accountability between physician and patient. Certainly the resources of medical societies should be used to call on legal and organizational experts to consider changes in the hospital "culture" that will best maintain the role of physicians in quality-of-care decisions and in the oversight of quality of care if hospital liability comes to pass.

What organizational changes will best meld physicians' interests with those of the hospital, so that physicians' professional autonomy can continue, and physicians, not administrators, more effectively monitor the work of medical staff? Can a new medical staff relationship promote physician loyalty and concern for hospital well-being while ensuring physician participation in the collective actions and voice of the hospital?

The introduction of "hospital culture" into the discussion is neither irreverent nor irrelevant. Proponents of corporate medicine note the "social insularity of the physician group," that "the physician profession-based culture may 'clash' with corporate culture," that "the conduct of physicians must be modified," that hospitals, among others, "are presently attempting to alter physician practice patterns," and that "managers can then establish organizational environments that effectively reduce the tension between cultures of the physician and the organization."[2]

I urge physicians to be adequately prepared to have an equal share in developing and guiding these new organizational environments. Now, while hospital liability is being discussed, and before it is implemented, is the time for physicians to consult with organizational and legal specialists who may best design a system that fosters the best provision of care, staff autonomy, oversight of colleagues' work, and accountability to patients and the community.

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Cocaine Toxicity in Glycogen Storage Disease

To the Editor: Cocaine has been implicated as a skeletal muscle toxin, producing nontraumatic rhabdomyolysis[1-3] or exacerbation of muscle weakness.[4] We report a case of a patient with previously diagnosed but asymptomatic glycogenosis who had prolonged respiratory muscle insufficiency after inhaling crack cocaine. This is the first report of such a case.

Report of a Case

The patient, a 26-year-old woman, was diagnosed at age 3 with glycogenosis type IIIA by muscle and liver biopsy in which the specimen showed an absence of glycogen debranching enzyme in both tissues. Before the current admission to hospital, she had had no clinical signs of muscle weakness, but had mildly elevated creatine kinase levels. She was admitted to the University Medical Center, Las Vegas, Nevada, in respiratory distress after several days of smoking crack cocaine. She was 16 weeks' pregnant. Her clinical condition worsened, necessitating intubation and mechanical ventilation. At this time she had shoulder girdle weakness, being unable to abduct her arms against minimal pressure. The chest radiograph showed bilateral, diffuse alveolar infiltration. Echocardiography revealed good contractile function. Her pulmonary capillary wedge pressure was normal. The patient's serum chemistry values were notable for a potassium level of 3.3 mmol per liter (normal, 3.5 to 5.5), aspartate aminotransferase 116 units per liter (normal, 5 to 35), creatine kinase 2,000 units per liter (normal, 35 to 230) without elevated levels of the myocardial-specific isoenzyme, triglycerides 3.10 mmol per liter (275 mg per dl [normal, 0.34 to 1.70]), and cholesterol 6.10 mmol per liter (236 mg per dl [normal, 3.65 to 5.20]). Serum levels of calcium, phosphorus, and magnesium were within normal limits. The urine myoglobin test was negative.

The patient's cocaine-induced pulmonary edema abated notably within two days of intubation, but she could not be weaned from mechanical ventilation. Attempts at weaning showed that she was unable to generate a static inspiratory pressure of 20 cm of water and maintained a respiratory rate of 30 to 40 breaths per minute to avoid hypercarbia. She remained on mechanical ventilation for 11 days before finally being able to breathe effectively on her own. Her creatine kinase serum level decreased to 1,150 units per liter before weaning from mechanical ventilation was possible.

The patient had a normal neonate by cesarean section after a pregnancy of nine months and was later lost to follow-up.

Discussion

Cocaine use unmasked the subclinical skeletal muscle weakness in our patient. Glycogenosis type III (Cori's disease) is an autosomal recessive glycogen storage disease caused by an inherited deficiency of glycogen debranching enzyme, with a resultant accumulation of

glycogen in the liver alone, type IIIB, or in liver and muscle tissue, type IIIA.[5-7] Persons with this condition can present in infancy with hypoglycemia, hepatomegaly, or, rarely, cardiac failure. Those with adult-onset disease, however, can be completely asymptomatic or have a progressive weakness of skeletal musculature.[6] Serum levels of muscle enzymes such as creatine kinase can be elevated even in asymptomatic persons with adult-onset glycogenosis type III. Others, such as our patient, with a deficiency of debranching enzyme in muscle are more likely to have myopathy and cardiomyopathy.[7]

Cocaine use has been responsible for nontraumatic rhabdomyolysis in several reports in which urine myoglobin was present,[1-3] which suggests that cocaine may have a direct lytic effect on skeletal muscle or that it produces muscle ischemia by vasospasm. It may also reduce myocyte excitability and subsequent tension generation[2] and has been implicated as a cause of impairment of neuromuscular transmission in a patient with myasthenia gravis.[4] Thus, several mechanisms by which cocaine exerts deleterious effects on skeletal muscle are likely. Cocaine abuse reduced the threshold whereby our patient's muscle weakness became clinically apparent, manifesting as respiratory muscular insufficiency.

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Advances in Cutaneous Laser Surgery

To the Editor: We were astonished to read the epitome in the April 1993 issue entitled "Laser Treatment of Skin Lesions" by Thomas R. Stevenson, MD.[1] The epitome was intended to be an update on firmly established treatment methods that are of clinical importance in laser surgery of cutaneous lesions. Unfortunately, it ignored some of the most important advances that have occurred in laser surgery in the past five years, specifically the use of the pulsed-dye laser for treating vascular lesions and Q-switched lasers for removing tattoos. Both of these lasers are based on the principles of selective photothermolysis as developed by Anderson and Parrish.[2]

The basic principles of this technique are to use a wavelength that will be selectively absorbed by the chromophore target of the lesion to be treated and to use a pulse width that is short enough to prevent nonselective thermal damage to the surrounding tissue. The flashlamp-pumped pulsed-dye laser, with a wavelength of 585 nm and a pulse width of 450 μsec, selectively targets vascular lesions, enabling the treatment of these lesions without the risk of scarring. Stevenson states that young children with port-wine stains are not good candidates for treatment because of the risk of scarring. This is indeed true if the argon laser is being used. The use of the pulsed-dye laser has revolutionized this therapy, however, as this laser is specifically designed for treating vessels that occur in infants and children having these capillary malformations. With this laser, the younger the child, the more effective is the treatment.[3] Infants can be readily treated without the risk of scarring. Early treatment of capillary hemangiomas is also effective with this laser, which will arrest the proliferative stage of the lesion, induce an involutional stage, and may prevent complications, scarring, and emotional distress associated with these lesions.[4]

Although both the neodymium:yttrium-aluminum-garnet (Nd:YAG) laser and the argon laser have been used successfully to treat capillary hemangiomas, the use of these lasers carries with it a substantial risk of scarring as a consequence of the nonspecific thermal damage that occurs.

Although the carbon dioxide laser has been used for many years to remove tattoos, this treatment invariably results in scarring, as the target of the laser is the skin containing the tattoo rather than the tattoo itself. No specific reaction occurs with the tattoo pigment, but rather a nonspecific thermal effect results in a slough of the tissue containing the pigment. In contrast, the Q-switched lasers—the Q-switched ruby,[5] Q-switched alexandrite,[6] and Q-switched Nd:YAG lasers—are targeted specifically to the tattoo pigment and result in fragmentation of the pigment into small particles that are picked up by macrophages and removed from the tissue.[7] No direct tissue interaction occurs, and as a consequence, tattoo removal can be accomplished without producing scar tissue. These lasers represent a tremendous technologic advance.

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Dr Stevenson Responds

To the Editor: The letter from Drs Fitzpatrick and Goldman in response to my epitome is appreciated.[1] My brief article was not written as a comprehensive review of laser therapy. My intent was to emphasize the fact that lasers are useful in treating skin lesions and tattoos. The results are often excellent, although not free of complications. I did omit a discussion of pulsed-dye lasers and the Q-switched pulsed ruby laser, both excellent tools. I thank the authors for a more complete review of the newest treatment techniques.

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Audible Third Heart Sound

To the Editor: I read with interest the article by Patel and colleagues regarding the audible third heart sound.[1] The authors selected an important clinical examination topic for review. They are to be commended for focusing on findings by "generalists" as opposed to "subspecialists" and for calculating test measures (true-positive and false-positive rates) at different cutoff points (ejection fractions < 50% and < 30%).

Their study has several methodologic problems that deserve to be mentioned, however. Interobserver variability was not reported. The authors state that the "cardiologist" examined a patient for a third heart sound when there was disagreement between the two "generalists." Interobserver variability could have easily been calculated.[2] This study also suffers from spectrum bias. Patients were selected for clinical examination after a decision had been made that the patient needed radionuclide ventriculography. No doubt the presence of heart failure and a third heart sound is more prevalent in this group than among general internists' patients. Such bias leads to an overestimation of true-positive rates and perhaps an underestimation of false-positive rates. As a result, the usefulness of the test is overestimated. Although an ideal study is difficult to carry out, its value should have been discussed by the authors. Patients in a general medicine setting should have been assessed at the bedside for jugular venous distension, hepatojugular reflux, rales, fourth heart sound, third heart sound, and peripheral edema. These patients should have had a posteroanterior x-ray film taken of the chest in addition to the gold standard test—radionuclide ventriculography. Test measures (true-positive and false-positive rates) could have been calculated to determine which individual bedside test or combination of tests is best for confirming or excluding cardiac dysfunction at different cutoff points.

I take issue with the authors' statement that, at an ejection fraction cutoff of less than 30%, the absence of an audible third heart sound excludes, with good confidence, severe cardiac dysfunction. The likelihood ratio negative (LR−) for a false-negative rate (0.22) and a true-negative rate (0.88) at an ejection fraction cutoff of less than 30% is 0.25. For pretest probabilities of 0.90, 0.70, 0.50, 0.30, and 0.10, the corresponding posttest probabilities with an LR− of 0.22 are 0.66, 0.34, 0.18, 0.09, and 0.02, respectively. It is doubtful that clinicians or patients would be reassured by a negative finding for a third heart sound unless the pretest probability was low. Thus, traditional thinking that an absence of an audible third heart sound does not rule out cardiac dysfunction is not challenged by the results of this study.

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Drs Sobotka and Bushnell Respond

To the Editor: We appreciate the thoughtful comments of Dr Nardone in response to our article.[1] The number of cases in which the initial two examiners disagreed regarding the presence of the third heart sound was approximately five. There is indeed an inherent spectrum bias introduced by selecting for correlation only those patients referred for nuclear ventriculography. This bias increases the population prevalence for severe heart failure and thus would tend to overestimate true-positive rates and underestimate false-positive rates. This "bias" is most appropriate, however, as the correlation would have less clinical meaning if applied to patients in whom the question of ventricular function was not relevant. The decision to refer patients to Nuclear Medicine in our hospital was routinely made by house staff in training to become general internists who care for patients admitted to general medicine services, and thus it reflects a patient sampling and physician interest for which the question is relevant.

Nardone appropriately suggests broadening the scope of our investigation to include the panorama of physical examination observations that historically are thought to document ventricular performance. This list includes, but is not exhausted by, jugular venous distension, hepatojugular reflux, rales, third heart sound, edema, hepatic size and pulsations, indirect definitive precordial percussion, apical pulsation location and size, Valsalva maneuver induction of pressure changes, and post-extrasystolic beat potentiation potential. The Evidence-Based Medicine Working Group has proposed that physical diagnostic maneuvers must meet criteria of accuracy and repro-

ducibility to support their rational use in the clinical setting.[2] In this regard, each physical examination technique must be tested to determine its accuracy and reproducibility with appropriate technologies.[3] Our article addresses just such a question—the value of the third heart sound as identified by the generalist.

Nardone is, of course, correct to point out the strong relationship between pretest probability and posttest probability (predictive values). We also mention in the article the dependence of predictive values on disease prevalence. We agree that the absence of the third heart sound is most useful to the clinician in those patients in whom the likelihood of severe heart failure is low. The prevalence of severe heart failure in internists' patients is low. Correspondingly, for a patient with a pretest likelihood of 30% or less (using an LR− of 0.22), there is greater than a 90% chance that severe heart failure is not present when the third heart sound is not heard. There may be little clinical value in obtaining radionuclide ventriculographic documentation of ventricular performance in patients with pretest probabilities of severe ventricular dysfunction of 0.7 to 0.9.

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Improving Drug Therapy in the Elderly

To the Editor: Dr Hobson, in her article, "Medications in Older Persons," in the November 1992 issue,[1] passes on some useful principles for prescribing for the elderly. If physicians follow these suggestions, their elderly patients may have fewer problems with medications. We would like to comment, however, on several statements made in the article.

Hobson's comment that lidocaine therapy should be started at a lower dose in the elderly is somewhat misleading. Abernathy and Greenblatt evaluated the pharmacokinetics of lidocaine in elderly and young subjects and suggested that it is appropriate to adjust the infusion rate but not the loading dose in the elderly.[2] It is interesting to note that the hepatic clearance was reduced in elderly men but not elderly women. The maintenance dose of lidocaine may need to be reduced in the elderly because of concurrent disease, such as congestive heart failure or reduced hepatic clearance of the drug. The suggestion to reduce the dose of H_2-receptor antagonists by 50% if the estimated creatinine clearance is less than 0.50 ml per second (30 ml per minute) needs more discussion because H_2-receptor antagonists do not have the same dosing guidelines for all patients with renal impairment. For example, a patient with a creatinine clearance below 0.83 ml per second (50 ml per minute) who is taking ranitidine hydrochloride (Zantac) should have the dose reduced to 150 mg every 24 hours (orally) and 50 mg every 18 to 24 hours if administered intramuscularly or intravenously. For those patients with a creatinine clearance of less than 0.50 ml per second, their cimetidine dosage should be reduced to 300 mg every 12 hours. A further decline in renal function will require additional dosage adjustments. Because these drugs are cleared both renally and hepatically, the dose should be adjusted downward if there is notable hepatic impairment.

In discussing benzodiazepines, Hobson refers to lorazepam as a shorter-acting agent and triazolam as a short-acting agent. The half-life of lorazepam is 10 to 20 hours, which is generally defined today as an intermediate-acting benzodiazepine. Triazolam, with a half-life of 2 to 6 hours in the elderly, is considered a short-acting benzodiazepine. To say that any of these drugs is "much safer" may be misleading because the elderly, especially those older than 75 years, are more "sensitive" to this family of medications.[3] All of these drugs can cause rebound anxiety, rebound insomnia, and paradoxical agitation.

We agree with Hobson's comment regarding the misuse of antipsychotic agents in elderly patients. Haloperidol (Haldol) is not a phenothiazine, as mentioned in the article, but a butyrophenone—which has minimal anticholinergic activity but does frequently cause extrapyramidal movement disorders.

While it is true that lean muscle mass declines with age, as reflected in Table 1 of the article, this is not the principal reason for increased levels of the given example of digoxin. Cusack and colleagues reported that "Raised steady-state serum concentrations of digoxin in the elderly are, therefore, mainly a function of reduced plasma clearance."[4] Increased steady-state serum levels of digoxin are more likely to occur in patients with impaired renal function.

As Hobson points out, "Adverse drug reactions are common in elderly patients, but often preventable." We agree and appreciate any efforts to increase physicians' awareness of the hazards of prescribing for patients older than 65 and especially for those older than 75 years. In this we think Hobson's article succeeds. We look forward to future articles that will assist physicians in selecting drug therapy for their older patients.

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EDITOR'S NOTE: *Dr Hobson chose not to respond to this letter.*

Why Physicians Retire Continued

TO THE EDITOR: I enjoyed "Physicians' Adjustment to Retirement" in the February issue.[1] As a recent retiree after 20 years in solo primary care practice, then 10 years in a health maintenance organization (HMO), I found myself typical of the 600 doctors interviewed: there is life after medicine! For those of you on the fence, read the article and go for it!

Although I appreciated that Virshup and Coombs stuck to the title in content, their response to Tepper's letter critical of their having avoided the reasons physicians retired was, in my opinion, hasty, perhaps inaccurate, and certainly incomplete.

They faulted "governmental intervention, skewed economic factors, and the emergence of HMOs." I personally found working for an HMO to be a pleasant and rewarding experience. Though gatekeeping is a newly coined term, it should have been part of a personal physician's duty and function long before HMOs emerged. In addition, malpractice is just as devastating and real a threat inside the HMO setting as outside.

Some of our own behavior as physicians has contributed to our discontent. Blatant advertising by lawyers, engineers, or physicians demeans the concept of "professional." This is but one example of our own actions that has contributed to our problems.

Let us point the finger at a variety of causes for discontent and early retirement of some of us, but let us include pointing to the mirror. We are not entirely blameless for some of our misery. Brings to mind: Physician, heal thyself.

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REFERENCES

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Access to Obstetric Care—The San Diego Experience

TO THE EDITOR: While Avid and colleagues have chosen an important and timely topic, we were disturbed by the methodology and implications of their article, "Barriers to Prenatal Care for Low-Income Women," in the May 1993 issue.[1] The authors, unfortunately, attempted to explore this complex problem through interviews of a few obstetrician-gynecologists and a patient survey instrument.

One must be cautious in accepting the implications regarding obstetrician-gynecologists. Apparently only four of the seven physicians interviewed were currently practicing obstetrics; two had quit obstetric practice, and one had moved to an administrative position. In addition, the authors did not state whether any of the physicians interviewed accept or have ever accepted pregnant Medi-Cal patients. Indeed, it would have been more productive to contrast attitudes between groups of obstetricians who do and do not accept Medi-Cal patients. In San Diego, those who do accept Medi-Cal patients cite ease of billing and rapidity of payment and the compliance and gratitude of patients and their families as some of the reasons that they provide these patients with prenatal services. Obtaining specialists for referrals is seldom an issue. In San Diego, rates of reimbursement and language barriers are cited as the most common problems in taking care of these patients.

The authors applied a survey questionnaire to the "No-Doc" patients, apparently without attempting to validate the responses. Were patients giving their real reasons for not having seen a physician, or were they giving reasons that they thought the surveyors wanted to hear? Did the patients wonder whether the survey was being used by county social services and whether the responses might be used to "take the baby away"?—a common concern voiced by our "No-Doc" patients.

Our perinatal group covers about 40% of "No-Doc" patients for a large community hospital in San Diego and consults for many more. For such patients, we involve our social work staff in exploring family and home situations and specifically ask why no prenatal care was obtained, to ensure that impediments to prenatal care do not translate into barriers to pediatric follow-up. Three patterns have been observed, and we suspect that they may apply in Sacramento as well.

- Some patients are uninsured and do not know about available resources such as Medi-Cal. In our region, most of these patients are recent arrivals to the United States and often have serious financial and language problems as well. Their prenatal care comes in emergency departments.
- Insured patients or patients with Medi-Cal sometimes say that they unsuccessfully tried to find a physician. In San Diego County, however, there are many obstetricians who take Medi-Cal as payment and several who will accept late registrants for care. The patient can virtually always find an obstetrician in the phone book or by calling the county medical society's referral line. When we explored this issue with English-speaking patients, external barriers to obtaining care were rare. Among the non–English-speaking patients, barriers in communication or access to information, transportation, or both, often existed.
- As the authors pointed out, a substantial proportion of "No-Doc" patients have drug problems. Those patients who use drugs such as "crank" or "crack" often blame outside influences in general and providers in particular for their failure to seek care, but generally have avoided

prenatal care either for fear of discovery or because of the all-consuming nature of their drug habits. Nearly all of the patients with drug problems whom we see speak English and have transportation. Most have either Medi-Cal or private insurance or are eligible for Medi-Cal but have not applied for benefits.

The authors concluded that "the results of this study show that the primary barrier to care . . . is finding a physician. . . ." We do not think this conclusion is justified. We do agree that "this population needs special support services to ensure adequate care," but it is crucial to recognize that "No-Doc" patients are not a homogenous group. Taxi vouchers, translators, and information would help recent immigrants; patients with a drug problem have very different needs, and English-speaking patients with Medi-Cal who choose not to see a physician present yet another challenge to the health care system.

Lack of prenatal care is a serious problem, but surveys such as the one published may obscure rather than clarify the situation. We invite the authors to come on down in the "trenches" with us and spend some time talking with these women and their families, instead of applying survey tools to them. And talk with obstetricians who provide prenatal care for Medi-Cal patients—we think they would be pleasantly surprised!

VAL CATANZARITE, MD, PhD
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REFERENCE

1. Aved BM, Irwin MM, Cummings LS, Findeisen N: Barriers to prenatal care for low-income women. West J Med 1993; 158:493-498

* * *

Dr Aved, Ms Irwin, Ms Cummings, and Ms Findeisen Respond

To the Editor: Catanzarite and White have described a county health system that, compared with many counties in California, is "user-friendly" to obstetric patients. We here in Sacramento are envious of the successful referral system that has been developed in San Diego County with the assistance of the American College of Obstetricians and Gynecologists, District IX. This has been possible, in large part, through generous grants from private foundations and other partners. We are also envious of the favorable political climate in their medical community that has encouraged such a large proportion of physicians to accept referrals of Medi-Cal patients—aided by the support services of their county-wide referral project.

Our article should have pointed out that two of the seven obstetrician-gynecologists interviewed currently accept patients with Medi-Cal; the other four practicing physicians had at one time taken Medi-Cal patients but no longer do so for the reasons cited. The will to adopt a county-wide strategy to address these reasons has not been as strong in our county as in the one described by Catanzarite and White. As they know, however, this situation is expected to change with California's plan to move Medi-Cal women into managed care systems.

On our method of interviewing patients, it seems that Catanzarite and White have missed the point that outreach workers and nurse practitioners (matched ethnically and linguistically where possible) from "the trenches" spent up to an hour talking with the women, asking them both open- and closed-ended questions. That this prompted women to volunteer information well beyond what might be expected—disclosure of drug use, fear of deportation—seems to provide some validation for the responses. Though we did not state this, the interviewers were clear in describing the purpose of the study to the women as trying to learn what keeps pregnant women from being able to get health care. Had we not done so, we agree that there could have been a distortion of survey results by the "interviewer factor."

While San Diego women may not experience the barriers to prenatal care—and thus deliver through emergency department admissions—to the same degree that women do in Sacramento County, the three "patterns" described by Catanzarite and White confirm the universality of these problems. What appear to be different are the programs that are in place in individual communities to overcome these barriers. Based on our survey of women in Sacramento who delivered through emergency departments with no physician of record, the inability to find physicians willing to accept Medi-Cal patients ranked as the top barrier. From the response to our article from the field, we are aware that we have hit a responsive chord about this important problem.

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Lessons From the Practice

The Wake-up Call

JOYCE ADAMS, MD, *Fresno, California*

The jangling of the telephone woke me from a sound sleep at 6 AM that day. Groping my way to the kitchen so as not to disturb my sleeping husband, I had a sense of dread. The rather desperate-sounding emergency department physician on the other end relayed the story to me. "The police brought in a little 3-year-old girl who was found wandering around outside an apartment complex. She's been beaten on the face and head, and her underpants are soaked with blood. We think she's been sodomized, but she's too terrified to let anyone even approach her and will probably need an examination under anesthesia. We'd like the most experienced person to do the exam." Pause. "Well," I thought, "I guess that's me." The image of a small, frightened child with bruises on her face, huddled bleeding in the corner of the examination room, having experienced God knows what at the hands of a brutal assailant, compelled me to respond.

Of course I would come in and do the examination. There are not many health care professionals who "specialize" in the examination of sexually abused children, and I was one. So I made the necessary arrangements, going about my usual morning routine, giving my sleepy-eyed 4-year-old son an extra-long hug; sitting on Mommy's lap, he did not notice my tears. The feelings of horror, grief, and rage welling up inside me had to be pushed down. I was the physician, the expert, the professional.

At the hospital, my mental image of the child was confirmed, except that she turned out to be 5 years old, not 3, and had calmed down somewhat after being reunited with her mother. She had been abducted from her apartment while the family slept, taken a few blocks away, raped, and left to wander. A neighbor had called the police. According to the detective, this was the seventh case in three months with this "M.O." They had no suspect in custody. Looking at the child, her face a mass of bruises, a blank look in her big dark eyes, I again had to put my emotional response on hold to be able to continue.

In some ways, it was easier doing this examination than most. Under general anesthesia, she did not have to be frightened by the police photographer snapping photographs of her bruises and the dried blood on her legs, or of the nurse who drew a blood specimen and gave her shots for tetanus and hepatitis, or of me, looking and probing, spreading her little buttocks to reveal the two deep tears in her anus. I was calm as I collected all the specimens for the rape kit, took my colposcopic photographs of the injuries, and filled out all the paperwork.

Even though I have examined hundreds of victims of child sexual abuse, the brutality of this case shook me to the core. What kind of person can violently sodomize a little child? Or is this even a "person"? It was beyond comprehension. This child's innocence, her trust, had been destroyed in an instant. Justice, in whatever form it would take, could never restore this child to wholeness.

Back at my office, I gave myself permission to fall apart for 30 minutes. It was not long enough. I was too busy to really fall apart; I had clinic that afternoon and a regional conference to chair the next two days, and I did it. I was the calm professional, in control, dedicated to teaching others about the problem of child abuse.

The conference was a success, but I did not feel happy or like I had accomplished anything important. The image of the little child who had been raped lingered in my mind. What will her future be like? Did it really matter that an "expert" examined her?

In the following days, I went on with my usual work, examining children with more "typical" histories: long-standing nonviolent molestation by fathers and stepfathers, which leaves no physical signs for my examination to detect. Another day was spent in court trying to explain to a judge why an adolescent's examination result would be normal and that her crystal-clear descriptions of abuse should be enough.

Returning from one such court case, I suddenly was physically weighted down by feelings of helplessness and hopelessness; I could barely stand or walk. I had to force myself to put one foot in front of the other, almost as if I were paralyzed. I knew that my body was trying to tell me that I had to stop for a while. I had to feel the pain, the grief, the anger, and the frustration of not being able to *do* anything.

People often say, when they find out what my specialty is, "I don't know how you do it." I'm beginning to ask myself: "*Why* do I do it?" There are certainly more fun ways to be a pediatrician. Why do people choose to work in areas of medicine that most find too depressing? What keeps us going? These are some of the questions I am struggling with, as I take a mental health break from

(Adams J: The wake-up call. West J Med 1993; 159:514-515)

From the Fresno-Central San Joaquin Valley Medical Education Program, University of California, San Francisco, School of Medicine, and the Department of Pediatrics, Valley Medical Center, Fresno, California.

Reprint requests to Joyce Adams, MD, Dept of Pediatrics, Valley Medical Center, 445 S Cedar Ave, Fresno, CA 93702.

my job. It is time to pay attention to my emotional pain and learn from it.

It has been three months since I had to take a week-long leave of absence. Writing out the details of this case and putting it aside helped me to deal with the feelings of hopelessness that overwhelmed me and caused my "mini-breakdown." I have thought a lot about why this patient in particular affected me so deeply, and it seems that it was like the last toy block added to a precarious tower, making the whole structure collapse.

Every time I see an abuse case and listen to the story and see the child's pain, I allow myself to feel some empathy, but I must suppress the full impact. I protect myself by immediately forgetting the child's name and details of the case, but all that information is still there in my mind. When I let this one child's pain get past my wall of defenses, all the other images of hurting, frightened, and shamed children came tumbling out.

I still have more questions than answers about why it is that I keep doing child abuse work, and the answers I come up with seem trite. I do it because it needs to be done, and I have a skill in a specialized area of medicine that is sometimes helpful in abuse cases. Sometimes—but not always. I cannot make a child's pain go away, and I need to acknowledge that.

I do not know how long I can continue doing this work. It helps to talk about my emotional response with other people who do child abuse work, but I am still ambivalent about my choosing this specialty.

Maybe we all need this kind of wake-up call, every now and then, to force us to take a look at what we do, and how, and why, and whether, after all, it is time to make a change.

* * *

"Lessons From the Practice" presents a personal experience of practicing physicians, residents, and medical students that made a lasting impression on the author. These pieces will speak to the art of medicine and to the primary goals of medical practice—to heal and to care for others. Physicians interested in contributing to the series are encouraged to submit their "lessons" to the series' editors.

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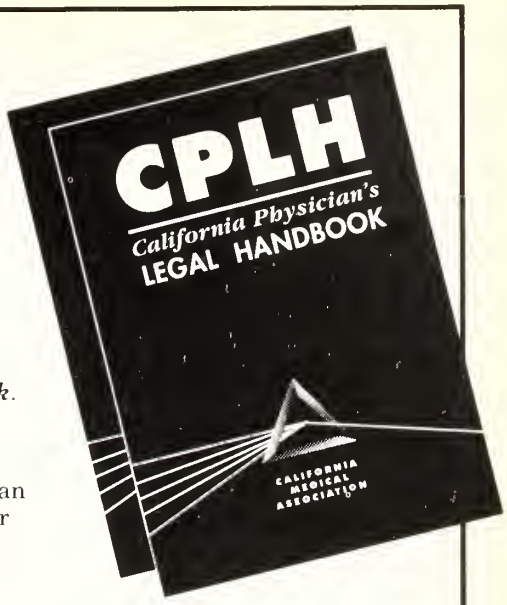

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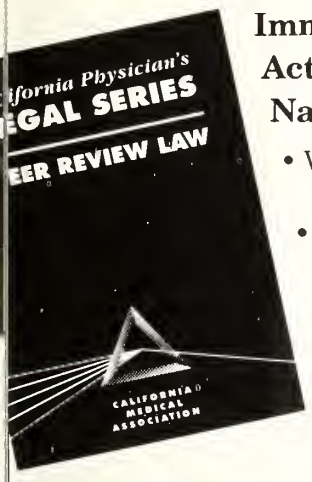

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Bode, Arnold G. H., Santa Ana. Died Jul 17, 1993, aged 81. Graduate of University of California, San Francisco, School of Medicine, 1938. Licensed in California in 1938. Dr Bode was a member of the Orange County Medical Association.

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Natale, Eugene, Los Angeles. Died Jun 25, 1993, aged 68. Graduate of U/Bern, Switzerland, 1965. Licensed in California in 1969. Dr Natale was a member of the Los Angeles County Medical Association.

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Thompson, James Douglas, San Jose. Died Jun 12, 1993, aged 51. Graduate of University of Kansas School of Medicine, Lawrence-Kansas City, 1974. Licensed in California in 1982. Dr Thompson was a member of the Santa Clara County Medical Association.

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Parnall, Edward, Albuquerque. Died May 26, 1993, aged 89. Graduate of Harvard University, Boston, Massachusetts, 1929. Licensed in New Mexico in 1946. Dr Parnall was a member of the Greater Albuquerque Medical Association.

Post, David B., Albuquerque. Died Jul 28, 1993, aged 70. Licensed in New Mexico in 1952. Dr Post was a member of the Greater Albuquerque Medical Association.

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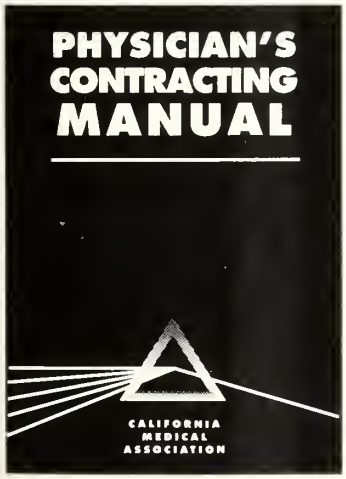

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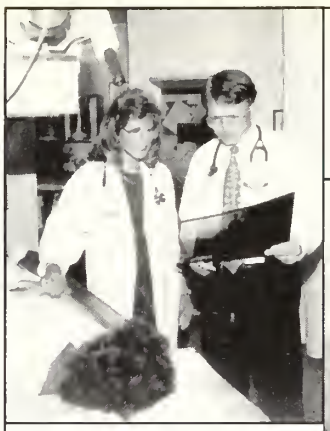

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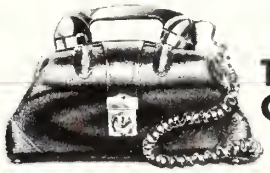

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Idaho Medical Association–305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888. Annual Meeting: July 28-30, 1994, Sun Valley.

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New Mexico Medical Society–7770 Jefferson NE, Suite 400, Albuquerque 87109. (505) 828-0237. Annual Meeting: May 5-7, 1994, Society Office, Albuquerque.

Utah Medical Association–540 E Fifth South, Salt Lake City 84102. (801) 355-7477. Annual Meeting: September 22-25, 1993, University Park Hotel, Salt Lake City.

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Reference: 1. Jones PH, et al. Once-daily pravastatin in patients with primary hypercholesterolemia: a dose-response study. *Clin Cardiol.* 1991,14:146-151

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WARNINGS

Liver Enzymes: HMG-CoA reductase inhibitors, like some other lipid-lowering therapies, have been associated with biochemical abnormalities of liver function. Increases of serum transaminase (ALT, AST) values to more than 3 times the upper limit of normal occurring on 2 or more (not necessarily sequential) occasions have been reported in 1.3% of patients treated with pravastatin in the U.S. over an average period of 18 months. These abnormalities were not associated with cholestasis and did not appear to be related to treatment duration. In those patients in whom these abnormalities were believed to be related to pravastatin and who were discontinued from therapy, the transaminase levels usually fell slowly to pretreatment levels. These biochemical findings are usually asymptomatic although worldwide experience indicates that anorexia, weakness, and/or abdominal pain may also be present in rare patients.

As with other lipid-lowering agents, liver function tests should be performed during therapy with pravastatin. Serum aminotransferases, including ALT (SGPT), should be monitored before treatment begins, every six weeks for the first three months, every eight weeks during the remainder of the first year, and periodically thereafter (e.g., at about six-month intervals). Special attention should be given to patients who develop increased transaminase levels. Liver function tests should be repeated to confirm an elevation and subsequently monitored at more frequent intervals. If increases in AST and ALT equal or exceed three times the upper limit of normal and persist, then therapy should be discontinued. Persistence of significant aminotransferase elevations following discontinuation of therapy may warrant consideration of liver biopsy.

Active liver disease or unexplained transaminase elevations are contraindications to the use of pravastatin (see CONTRAINDICATIONS). Caution should be exercised when pravastatin is administered to patients with a history of liver disease or heavy alcohol ingestion (see CLINICAL PHARMACOLOGY: Pharmacokinetics/Metabolism). Such patients should be closely monitored, started at the lower end of the recommended dosing range, and titrated to the desired therapeutic effect.

Skeletal Muscle: Rhabdomyolysis with renal dysfunction secondary to myoglobinuria has been reported with pravastatin and other drugs in this class. Uncomplicated myalgia has also been reported in pravastatin-treated patients (see ADVERSE REACTIONS). Myopathy, defined as muscle aching or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values to greater than 10 times the upper limit of normal was reported to be possibly due to pravastatin in only one patient in clinical trials (<0.1%). Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. **Pravastatin therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected. Pravastatin therapy should also be temporarily withheld in any patient experiencing an acute or serious condition predisposing to the development of renal failure secondary to rhabdomyolysis, e.g., sepsis; hypotension; major surgery; trauma; severe metabolic, endocrine, or electrolyte disorders; or uncontrolled epilepsy.**

The risk of myopathy during treatment with lovastatin is increased if therapy with either cyclosporine, gemfibrozil, erythromycin, or niacin is administered concurrently. There is no experience with the use of pravastatin together with cyclosporine. Myopathy has not been observed in clinical trials involving small numbers of patients who were treated with pravastatin together with niacin. One trial of limited size involving combined therapy with pravastatin and gemfibrozil showed a trend toward more frequent CPK elevations and patient withdrawals due to musculoskeletal symptoms in the group receiving combined treatment as compared with the groups receiving placebo, gemfibrozil, or pravastatin monotherapy. Myopathy was not reported in this trial (see PRECAUTIONS: Drug Interactions). One patient developed myopathy when clofibrate was added to a previously well tolerated regimen of pravastatin; the myopathy resolved when clofibrate therapy was stopped and pravastatin treatment continued. **The use of fibrates alone may occasionally be associated with myopathy. The combined use of pravestatin and fibrates should generally be avoided.**

PRECAUTIONS

General: Pravastatin may elevate creatine phosphokinase and transaminase levels (see ADVERSE REACTIONS). This should be considered in the differential diagnosis of chest pain in a patient on therapy with pravastatin.

Homozygous Familial Hypercholesterolemia. Pravastatin has not been evaluated in patients with rare homozygous familial hypercholesterolemia. In this group of patients, it has been reported that HMG-CoA reductase inhibitors are less effective because the patients lack functional LDL receptors.

Renal Insufficiency. A single 20 mg oral dose of pravastatin was administered to 24 patients with varying degrees of renal impairment (as determined by creatinine clearance). No effect was observed on the pharmacokinetics of pravastatin or its 3α-hydroxy isomeric metabolite (SQ 31,906). A small increase was seen in mean AUC values and half-life (t1/2) for the inactive enzymatic ring hydroxylation metabolite (SQ 31,945). Given this small sample size, the dosage administered, and the degree of individual variability, patients with renal impairment who are receiving pravastatin should be closely monitored.

Information for Patients: Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever.

Drug Interactions: *Immunosuppressive Drugs, Gemfibrozil, Niacin (Nicotinic Acid), Erythromycin.* See WARNINGS: Skeletal Muscle.

Antipyrine: Clearance by the cytochrome P450 system was unaltered by concomitant administration of pravastatin. Since pravastatin does not appear to induce hepatic drug-metabolizing enzymes, it is not expected that any significant interaction of pravastatin with other drugs (e.g., phenytoin, quinidine) metabolized by the cytochrome P450 system will occur.

Cholestyramine/Colestipol: Concomitant administration resulted in an approximately 40 to 50% decrease in the mean AUC of pravastatin. However, when pravastatin was administered 1 hour before or 4 hours after cholestyramine or 1 hour before colestipol and a standard meal, there was no clinically significant decrease in bioavailability or therapeutic effect. (See DOSAGE AND ADMINISTRATION: Concomitant Therapy.)

Warfarin: In a study involving 10 healthy male subjects given pravastatin and warfarin concomitantly for 6 days, bioavailability parameters at steady state for pravastatin (parent compound) were not altered. Pravastatin did not alter the plasma protein-binding of warfarin. Concomitant dosing did increase the AUC and Cmax of warfarin but did not produce any changes in its anticoagulant action (i.e., no increase was seen in mean prothrombin time after 6 days of concomitant therapy). However, bleeding and extreme prolongation of prothrombin time has been reported with another drug in this class. Patients receiving warfarin-type anticoagulants should have their prothrombin times closely monitored when pravastatin is initiated or the dosage of pravastatin is changed.

Cimetidine: The AUC_{0-12hr} for pravastatin when given with cimetidine was not significantly different from the AUC for pravastatin when given alone. A significant difference was observed between the AUC's for pravastatin when given with cimetidine compared to when administered with antacid.

Digoxin. In a crossover trial involving 18 healthy male subjects given pravastatin and digoxin concurrently for 9 days, the bioavailability parameters of digoxin were not affected. The AUC of pravastatin tended to increase, but the overall bioavailability of pravastatin plus its metabolites SQ 31,906 and SQ 31,945 was not altered.

Gemfibrozil: In a crossover study in 20 healthy male volunteers given concomitant single doses of pravastatin and gemfibrozil, there was a significant decrease in urinary excretion and protein binding of pravastatin. In addition, there was a significant increase in AUC, Cmax, and Tmax for the pravastatin metabolite SQ 31,906. Combination therapy with pravastatin and gemfibrozil is generally not recommended.

In interaction studies with *aspirin, antacids* [1 hour prior to PRAVACHOL (pravastatin sodium)], *cimetidine, nicotinic acid,* or *probucol,* no statistically significant differences in bioavailability were seen when PRAVACHOL was administered.

Other Drugs: During clinical trials, no noticeable drug interactions were reported when PRAVACHOL was added to: diuretics, antihypertensives, digitalis, converting-enzyme inhibitors, calcium channel blockers, beta-blockers, or nitroglycerin.

Endocrine Function: HMG-CoA reductase inhibitors interfere with cholesterol synthesis and lower circulating cholesterol levels and, as such, might theoretically blunt adrenal or gonadal steroid hormone production. Results of clinical trials with pravastatin in males and post-menopausal females were inconsistent with regard to possible effects of the drug on basal steroid hormone levels. In a study of 21 males, the mean testosterone response to human chorionic gonadotropin was significantly reduced ($p<0.004$) after 16 weeks of treatment with 40 mg of pravastatin. However, the percentage of patients showing a ≥50% rise in plasma testosterone after human chorionic gonadotropin stimulation did not change significantly after therapy in these patients. The effects of HMG-CoA reductase inhibitors on spermatogenesis and fertility have not been studied in adequate numbers of patients. The effects, if any, of pravastatin on the pituitary-gonadal axis in pre-menopausal females are unknown. Patients treated with pravastatin who display clinical evidence of endocrine dysfunction should be evaluated appropriately. Caution should also be exercised if an HMG-CoA reductase inhibitor or other agent used to lower cholesterol levels is administered to patients also receiving other drugs (e.g., ketoconazole, spironolactone, cimetidine) that may diminish the levels or activity of steroid hormones.

CNS Toxicity: CNS vascular lesions, characterized by perivascular hemorrhage and edema and mononuclear cell infiltration of perivascular spaces, were seen in dogs treated with pravastatin at a dose of 25 mg/kg/day, a dose that produced a plasma drug level about 50 times higher than the mean drug level in humans taking 40 mg/day. Similar CNS vascular lesions have been observed with several other drugs in this class.

A chemically similar drug in this class produced optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in clinically normal dogs in a dose-dependent fashion starting at 60 mg/kg/day, a dose that produced mean plasma drug levels about 30 times higher than the mean drug level in humans taking the highest recommended dose (as measured by total enzyme inhibitory activity). This same drug also produced vestibulocochlear Wallerian-like degeneration and retinal ganglion cell chromatolysis in dogs treated for 14 weeks at 180 mg/kg/day, a dose which resulted in a mean plasma drug level similar to that seen with the 60 mg/kg dose.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a 2-year study in rats fed pravastatin at doses of 10, 30, or 100 mg/kg body weight, there was an increased incidence of hepatocellular carcinomas in males at the highest dose ($p<0.01$). Although rats were given up to 125 times the human dose (HD) on a mg/kg body weight basis, their serum drug levels were only 6 to 10 times higher than those measured in humans given 40 mg pravastatin as measured by AUC.

The oral administration of 10, 30, or 100 mg/kg (producing plasma drug levels approximately 0.5 to 5.0 times human drug levels at 40 mg) of pravastatin to mice for 22 months resulted in a statistically significant increase in the incidence of malignant lymphomas in treated females when all treatment groups were pooled and compared to controls ($p<0.05$). The incidence was not dose-related and male mice were not affected.

A chemically similar drug in this class was administered to mice for 72 weeks at 25, 100, and 400 mg/kg body weight, which resulted in mean serum drug levels approximately 3, 15, and 33 times higher than the mean human serum drug concentration (as total inhibitory activity) after a 40 mg oral dose. Liver carcinomas were significantly increased in high-dose females and mid- and high-dose males, with a maximum incidence of 90 percent in males. The incidence of adenomas of the liver was significantly increased in mid- and high-dose females. Drug treatment also significantly increased the incidence of lung adenomas in mid- and high-dose males and females. Adenomas of the eye Harderian gland (a gland of the eye of rodents) were significantly higher in high-dose mice than in controls.

No evidence of mutagenicity was observed *in vitro*, with or without rat-liver metabolic activation, in the following studies: microbial mutagen tests, using mutant strains of *Salmonella typhimurium* or *Escherichia coli*, a forward mutation assay in L5178Y TK +/− mouse lymphoma cells, a chromosomal aberration test in hamster cells, and a gene conversion assay using *Saccharomyces cerevisiae*. In addition, there was no evidence of mutagenicity in either a dominant lethal test in mice or a micronucleus test in mice.

In a study in rats, with daily doses up to 500 mg/kg, pravastatin did not produce any adverse effects on fertility or general reproductive performance. However, in a study with another HMG-CoA reductase inhibitor, there was decreased fertility in male rats treated for 34 weeks at 25 mg/kg body weight, although this effect was not observed in a subsequent fertility study when this same dose was administered for 11 weeks (the entire cycle of spermatogenesis, including epididymal maturation). In rats treated with this same reductase inhibitor at 180 mg/kg/day, seminiferous tubule degeneration (necrosis and loss of spermatogenic epithelium) was observed. Although not seen with pravastatin, two similar drugs in this class caused drug-related testicular atrophy, decreased spermatogenesis, spermatocytic degeneration, and giant cell formation in dogs. The clinical significance of these findings is unclear.

Pregnancy: Pregnancy Category X: See CONTRAINDICATIONS.

Safety in pregnant women has not been established. Pravastatin was not teratogenic in rats at doses up to 1000 mg/kg daily or in rabbits at doses of up to 50 mg/kg daily. These doses resulted in 20x (rabbit) or 240x (rat) the human exposure based on surface area (mg/meter^2). However, in studies with another HMG-CoA reductase inhibitor, skeletal malformations were observed in rats and mice. PRAVACHOL (pravastatin sodium) should be administered to women of child-bearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards. If the woman becomes pregnant while taking PRAVACHOL, it should be discontinued and the patient advised again as to the potential hazards to the fetus.

Nursing Mothers: A small amount of pravastatin is excreted in human breast milk. Because of the potential for serious adverse reactions in nursing infants, women taking PRAVACHOL should not nurse (see CONTRAINDICATIONS).

Pediatric Use: Safety and effectiveness in individuals less than 18 years old have not been established. Hence, treatment in patients less than 18 years old is not recommended at this time. (See also PRECAUTIONS: **General**.)

ADVERSE REACTIONS

Pravastatin is generally well tolerated, adverse reactions have usually been mild and transient. In 4-month long placebo-controlled trials, 1.7% of pravastatin-treated patients and 1.2% of placebo-treated patients were discontinued from treatment because of adverse experiences attributed to study drug therapy, this difference was not statistically significant. In long-term studies, the most common reasons for discontinuation were asymptomatic serum transaminase increases and mild, non-specific gastrointestinal complaints. During clinical trials the overall incidence of adverse events in the elderly was not different from the incidence observed in younger patients.

Adverse Clinical Events: All adverse clinical events (regardless of attribution) reported in more than 2% of pravastatin-treated patients in the placebo-controlled trials are identified in the table below; also shown are the percentages of patients in whom these medical events were believed to be related or possibly related to the drug:

	All Events %		Events Attributed to Study Drug %	
Body System/Event	Pravastatin (N = 900)	Placebo (N = 411)	Pravastatin (N = 900)	Placebo (N = 411)
Cardiovascular				
Cardiac Chest Pain	4.0	3.4	0.1	0.0
Dermatologic				
Rash	4.0*	1.1	1.3	0.9
Gastrointestinal				
Nausea/Vomiting	7.3	7.1	2.9	3.4
Diarrhea	6.2	5.6	2.0	1.9
Abdominal Pain	5.4	6.9	2.0	3.9
Constipation	4.0	7.1	2.4	5.1
Flatulence	3.3	3.6	2.7	3.4
Heartburn	2.9	1.9	2.0	0.7
General				
Fatigue	3.8	3.4	1.9	1.0
Chest Pain	3.7	1.9	0.3	0.2
Influenza	2.4*	0.7	0.0	0.0
Musculoskeletal				
Localized Pain	10.0	9.0	1.4	1.5
Myalgia	2.7	1.0	0.6	0.0
Nervous System				
Headache	6.2	3.9	1.7*	0.2
Dizziness	3.3	3.2	1.0	0.5
Renal/Genitourinary				
Urinary Abnormality	2.4	2.9	0.7	1.2
Respiratory				
Common Cold	7.0	6.3	0.0	0.0
Rhinitis	4.0	4.1	0.1	0.0
Cough	2.6	1.7	0.1	0.0

*Statistically significantly different from placebo.

The following effects have been reported with drugs in this class:

Skeletal: myopathy, rhabdomyolysis.

Neurological: dysfunction of certain cranial nerves (including alteration of taste, impairment of extra-ocular movement, facial paresis), tremor, vertigo, memory loss, paresthesia, peripheral neuropathy, peripheral nerve palsy.

Hypersensitivity Reactions: An apparent hypersensitivity syndrome has been reported rarely which has included one or more of the following features: anaphylaxis, angioedema, lupus erythematous-like syndrome, polymyalgia rheumatica, vasculitis, purpura, thrombocytopenia, leukopenia, hemolytic anemia, positive ANA, ESR increase, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever, chills, flushing, malaise, dyspnea, toxic epidermal necrolysis, erythema multiforme, including Stevens-Johnson syndrome.

Gastrointestinal: pancreatitis, hepatitis, including chronic active hepalitis, cholestatic jaundice, fatty change in liver, and, rarely, cirrhosis, fulminant hepatic necrosis, and hepatoma, anorexia, vomiting.

Reproductive: gynecomastia, loss of libido, erectile dysfunction.

Eye: progression of cataracts (lens opacities), ophthalmoplegia.

Laboratory Test Abnormalities: Increases in serum transaminase (ALT, AST) values and CPK have been observed (see WARNINGS).

Transient, asymptomatic eosinophilia has been reported. Eosinophil counts usually returned to normal despite continued therapy. Anemia, thrombocytopenia, and leukopenia have been reported with other HMG-CoA reductase inhibitors.

Concomitant Therapy: Pravastatin has been administered concurrently with cholestyramine, colestipol, nicotinic acid, probucol and gemfibrozil. Preliminary data suggest that the addition of either probucol or gemfibrozil to therapy with lovastatin or pravastatin is **not** associated with greater reduction in LDL-cholesterol than that achieved with lovastatin or pravastatin alone. No adverse reactions unique to the combination or in addition to those previously reported for each drug alone have been reported. Myopathy and rhabdomyolysis (with or without acute renal failure) have been reported when another HMG-CoA reductase inhibitor was used in combination with immunosuppressive drugs, gemfibrozil, erythromycin, or lipid-lowering doses of nicotinic acid. Concomitant therapy with HMG-CoA reductase inhibitors and these agents is generally not recommended. (See WARNINGS: **Skeletal Muscle** and PRECAUTIONS: **Drug Interactions.**)

OVERDOSAGE

There have been no reports of overdoses with pravastatin.

Should an accidental overdose occur, treat symptomatically and institute supportive measures as required.

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THE PRAVACHOL® DIRECTION IN LIPID MANAGEMENT

Effective lipid management doesn't have to be tough

- Improves key lipids — significant reduction in LDL-C[1]
- Excellent safety profile
- Easy for patients — once-daily dosing, well tolerated
- Usual dose: 20 mg once daily at bedtime, with or without food

PRAVACHOL®

pravastatin sodium 20 mg tablets

PRAVACHOL is indicated as an adjunct to diet for the reduction of elevated total and LDL-cholesterol levels in patients with primary hypercholesterolemia (Types IIa and IIb) when the response to diet alone has not been adequate.

Active liver disease or unexplained transaminase elevations, pregnancy and lactation are contraindications to the use of pravastatin sodium.

Please see CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS in the brief summary of prescribing information on the adjacent page.

Bristol-Myers Squibb Company

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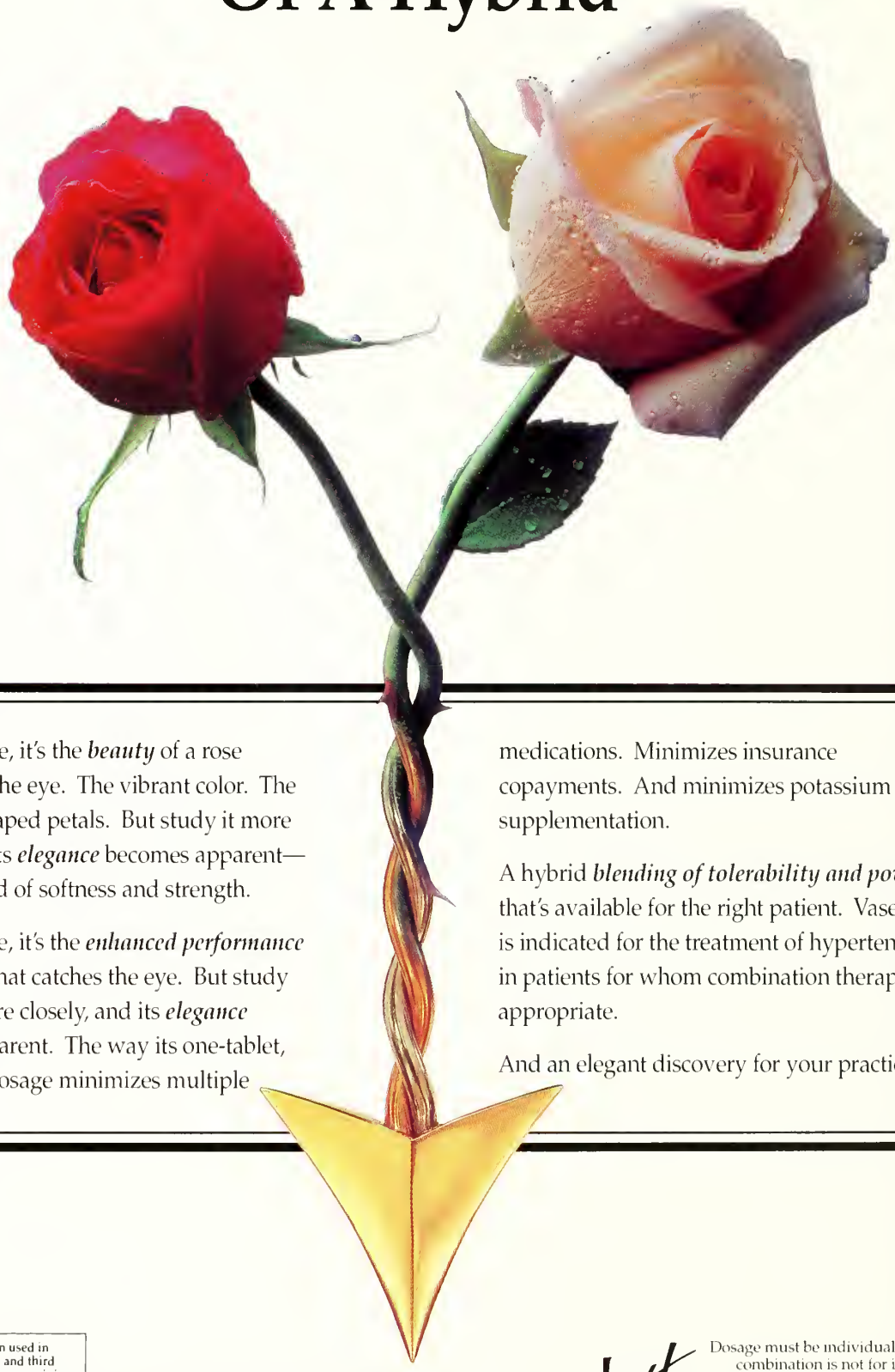
Second Class

Discover The Elegance Of A Hybrid



At first glance, it's the ***beauty*** of a rose that catches the eye. The vibrant color. The delicately shaped petals. But study it more closely, and its ***elegance*** becomes apparent—a gentle blend of softness and strength.

At first glance, it's the ***enhanced performance*** of Vaseretic that catches the eye. But study Vaseretic more closely, and its ***elegance*** becomes apparent. The way its one-tablet, once-a-day dosage minimizes multiple medications. Minimizes insurance copayments. And minimizes potassium supplementation.

A hybrid ***blending of tolerability and power*** that's available for the right patient. Vaseretic is indicated for the treatment of hypertension in patients for whom combination therapy is appropriate.

And an elegant discovery for your practice.

USE IN PREGNANCY: When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, Vaseretic® (Enalapril Maleate-Hydrochlorothiazide) should be discontinued as soon as possible. See WARNINGS, *Fetal/Neonatal Morbidity and Mortality*

VASERETIC® 10-25 *Next*
Enalapril Maleate-Hydrochlorothiazide

Dosage must be individualized; the fixed combination is not for initial therapy.

Evaluation of the hypertensive patient should always include assessment of renal function.

For a Brief Summary of Prescribing Information, see adjacent pages.

TABLETS
VASERETIC®
(ENALAPRIL MALEATE-HYDROCHLOROTHIAZIDE)

USE IN PREGNANCY: When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, VASERETIC® (Enalapril Maleate-Hydrochlorothiazide) should be discontinued as soon as possible. See WARNINGS, *Fetal/Neonatal Morbidity and Mortality*

CONTRAINDICATIONS: VASERETIC is contraindicated in patients who are hypersensitive to any component of this product and in patients with a history of angioedema related to previous treatment with an angiotensin converting enzyme inhibitor. Because of the hydrochlorothiazide component, this product is contraindicated in patients with anuria or hypersensitivity to other sulfonamide-derived drugs.

WARNINGS: *General, Enalapril Maleate, Hypotension:* Excessive hypotension was rarely seen in uncomplicated hypertensive patients but is a possible consequence of enalapril use in severely salt/volume depleted persons such as those treated vigorously with diuretics or patients on dialysis.

Syncope has been reported in 1-3 percent of patients receiving VASERETIC. In patients receiving enalapril alone, the incidence of syncope is 0.5 percent. The overall incidence of syncope may be reduced by proper titration of the individual components. (See PRECAUTIONS, *Drug Interactions*, and ADVERSE REACTIONS.)

In patients with severe congestive heart failure, with or without associated renal insufficiency, excessive hypotension has been observed and may be associated with oliguria and/or progressive azotemia, and rarely with acute renal failure and/or death. Because of the potential fall in blood pressure in these patients, therapy should be started under very close medical supervision. Such patients should be followed closely for the first two weeks of treatment and whenever the dose of enalapril and/or diuretic is increased. Similar considerations may apply to patients with ischemic heart or cerebrovascular disease, in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident.

If hypotension occurs, the patient should be placed in the supine position and, if necessary, receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses, which usually can be given without difficulty once the blood pressure has increased after volume expansion.

Angioedema: Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported in patients treated with angiotensin converting enzyme inhibitors, including enalapril. In such cases VASERETIC should be promptly discontinued and appropriate therapy and monitoring should be provided until complete and sustained resolution of signs and symptoms has occurred. In instances where swelling has been confined to the face and lips the condition has generally resolved without treatment, although antihistamines have been useful in relieving symptoms. Angioedema associated with laryngeal edema may be fatal. **Where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, appropriate therapy, e.g., subcutaneous epinephrine solution 1:1000 (0.3 mL to 0.5 mL) and/or measures necessary to ensure a patent airway, should be promptly provided.** (See ADVERSE REACTIONS.)

Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor (see also CONTRAINDICATIONS).

Neutropenia/Agranulocytosis: Another angiotensin converting enzyme inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression, rarely in uncomplicated patients but more frequently in patients with renal impairment especially if they also have a collagen vascular disease. Available data from clinical trials of enalapril are insufficient to show that enalapril does not cause agranulocytosis at similar rates. Marketing experience has revealed several cases of neutropenia or agranulocytosis in which a causal relationship to enalapril cannot be excluded. Periodic monitoring of white blood cell counts in patients with collagen vascular disease and renal disease should be considered.

Hydrochlorothiazide: Thiazides should be used with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. Cumulative effects of the drug may develop in patients with impaired renal function.

Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.

Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma.

The possibility of exacerbation or activation of systemic lupus erythematosus has been reported.

Lithium generally should not be given with thiazides (see PRECAUTIONS, *Drug Interactions, Enalapril Maleate and Hydrochlorothiazide*).

Pregnancy: Enalapril-Hydrochlorothiazide: There was no teratogenicity in rats given up to 90 mg/kg/day of enalapril (150 times the maximum human dose) in combination with 10 mg/kg/day of hydrochlorothiazide (2 ½ times the maximum human dose) or in mice given up to 30 mg/kg/day of enalapril (50 times the maximum human dose) in combination with 10 mg/kg/day of hydrochlorothiazide (2 ½ times the maximum human dose). At these doses, fetotoxicity expressed as a decrease in average fetal weight occurred in both species. No fetotoxicity occurred at lower doses, 30/10 mg/kg/day of enalapril-hydrochlorothiazide in rats and 10/10 mg/kg/day of enalapril-hydrochlorothiazide in mice.

When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, VASERETIC should be discontinued as soon as possible. (See *Enalapril Maleate, Fetal/Neonatal Morbidity and Mortality*, below.)

Enalapril Maleate, Fetal/Neonatal Morbidity and Mortality: ACE inhibitors can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature. When pregnancy is detected, ACE inhibitors should be discontinued as soon as possible.

The use of ACE inhibitors during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to the ACE-inhibitor exposure.

These adverse effects do not appear to have resulted from intrauterine ACE-inhibitor exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to ACE inhibitors only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should make every effort to discontinue the use of VASERETIC as soon as possible.

Rarely (probably less often than once in every thousand pregnancies), no alternative to ACE inhibitors will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intraamniotic environment.

If oligohydramnios is observed, VASERETIC should be discontinued unless it is considered lifesaving for the mother. Contraction stress testing (CST), a non-stress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of *in utero* exposure to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function. Enalapril, which crosses the placenta, has been removed from neonatal circulation by peritoneal dialysis with some clinical benefit, and theoretically may be removed by exchange transfusion, although there is no experience with the latter procedure.

No teratogenic effects of enalapril were seen in studies of pregnant rats and rabbits. On a mg/kg basis, the doses used were up to 333 times (in rats) and 50 times (in rabbits) the maximum recommended human dose.

Hydrochlorothiazide, Teratogenic Effects: Reproduction studies in the rabbit, the mouse and the rat at doses up to 100 mg/kg/day (50 times the human dose) showed no evidence of external abnormalities of the fetus due to hydrochlorothiazide. Hydrochlorothiazide given in a two-litter study in rats at doses of 4 - 5.6 mg/kg/day (approximately 1 - 2 times the usual daily human dose) did not impair fertility or produce birth abnormalities in the offspring. Thiazides cross the placental barrier and appear in cord blood.

Nonteratogenic Effects: These may include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult.

PRECAUTIONS: *General, Enalapril Maleate, Impaired Renal Function:* As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe congestive heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with angiotensin converting enzyme inhibitors, including enalapril, may be associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death.

In clinical studies in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine were observed in 20 percent of patients. These increases were almost always reversible upon discontinuation of enalapril and/or diuretic therapy. In such patients renal function should be monitored during the first few weeks of therapy.

Some patients with hypertension or heart failure with no apparent preexisting renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when enalapril has been given concomitantly with a diuretic. This is more likely to occur in patients with pre-existing renal impairment. Dosage reduction of enalapril and/or discontinuation of the diuretic may be required.

Evaluation of the hypertensive patient should always include assessment of renal function.

Hemodialysis Patients: Anaphylactoid reactions have been reported in patients dialyzed with high-flux membranes (e.g., AN 69*) and treated concomitantly with an ACE inhibitor. In these patients consideration should be given to using a different type of dialysis membrane or a different class of antihypertensive agent.

Hyperkalemia: Elevated serum potassium (greater than 5.7 mEq/L) was observed in approximately one percent of hypertensive patients in clinical trials treated with enalapril alone. In most cases these were isolated values which resolved despite continued therapy, although hyperkalemia was a cause of discontinuation of therapy in 0.28 percent of hypertensive patients. Hyperkalemia was less frequent (approximately 0.1 percent) in patients treated with enalapril plus hydrochlorothiazide. Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with enalapril. (See *Drug Interactions*.)

Cough: Cough has been reported with the use of ACE inhibitors. Characteristically, the cough is nonproductive, persistent and resolves after discontinuation of therapy. ACE inhibitor-induced cough should be considered as part of the differential diagnosis of cough.

Surgery/Anesthesia: In patients undergoing major surgery or during anesthesia with agents that produce hypotension, enalapril may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Hydrochlorothiazide: Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals. All patients receiving thiazide therapy should be observed for clinical signs of fluid or electrolyte imbalance: hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Warning signs or symptoms of fluid and electrolyte imbalance, irrespective of cause, include dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, confusion, seizures, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting.

Hypokalemia may develop, especially with brisk diuresis, when severe cirrhosis is present, or after prolonged therapy. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Hypokalemia may cause cardiac arrhythmia and may also sensitize or exaggerate the response of the heart to the toxic effects of digitalis (e.g., increased ventricular irritability). Because enalapril reduces the production of aldosterone, concomitant therapy with enalapril attenuates the diuretic-induced potassium loss (see *Drug Interactions, Agents Increasing Serum Potassium*).

Although any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease), chloride replacement may be required in the treatment of metabolic alkalosis.

Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction, rather than administration of salt except in rare instances when the hyponatremia is life-threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Hyperuricemia may occur or frank gout may be precipitated in certain patients receiving thiazide therapy.

In diabetic patients dosage adjustments of insulin or oral hypoglycemic agents may be required. Hyperglycemia may occur with thiazide diuretics. Thus latent diabetes mellitus may become manifest during thiazide therapy.

The antihypertensive effects of the drug may be enhanced in the postsympathectomy patient.

If progressive renal impairment becomes evident, consider withholding or discontinuing diuretic therapy.

Thiazides have been shown to increase the urinary excretion of magnesium; this may result in hypomagnesemia.

Thiazides may decrease urinary calcium excretion. Thiazides may cause intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

Increases in cholesterol and triglyceride levels may be associated with thiazide diuretic therapy.

Information for Patients, Angioedema: Angioedema, including laryngeal edema, may occur especially following the first dose of enalapril. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, extremities, eyes, lips, tongue, difficulty in swallowing or breathing) and to take no more drug until they have consulted with the prescribing physician.

Hypotension: Patients should be cautioned to report lightheadedness especially during the first few days of therapy. If actual syncope occurs, the patients should be told to discontinue the drug until they have consulted with the prescribing physician.

All patients should be cautioned that excessive perspiration and dehydration may lead to an excessive fall in blood pressure because of reduction in fluid volume. Other causes of volume depletion such as vomiting or diarrhea may also lead to a fall in blood pressure; patients should be advised to consult with the physician.

Hyperkalemia: Patients should be told not to use salt substitutes containing potassium without consulting their physician.

Neutropenia: Patients should be told to report promptly any indication of infection (e.g., sore throat, fever) which may be a sign of neutropenia.

Pregnancy: Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to ACE inhibitors, and they should also be told that these consequences do not appear to have resulted from intrauterine ACE-inhibitor exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.

NOTE: As with many other drugs, certain advice to patients being treated with VASERETIC is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Drug Interactions, Enalapril Maleate, Hypotension—Patients on Diuretic Therapy: Patients on diuretics and especially those in whom diuretic therapy was recently instituted, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with enalapril. The possibility of hypotensive effects with enalapril can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with enalapril. If it is necessary to continue the diuretic, provide medical supervision for at least two hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS.)

Agents Causing Renin Release: The antihypertensive effect of enalapril is augmented by antihypertensive agents that cause renin release (e.g., diuretics).

Other Cardiovascular Agents: Enalapril has been used concomitantly with beta adrenergic-blocking agents, methyldopa, nitrates, calcium-blocking agents, hydralazine and prazosin without evidence of clinically significant adverse interactions.

Agents Increasing Serum Potassium: Enalapril attenuates diuretic-induced potassium loss. Potassium-sparing diuretics (e.g., spironolactone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium. Therefore, if concomitant use of these agents is indicated because of demonstrated hypokalemia they should be used with caution and with frequent monitoring of serum potassium.

Lithium: Lithium toxicity has been reported in patients receiving lithium concomitantly with drugs which cause elimination of sodium, including ACE inhibitors. A few cases of lithium toxicity have been reported in patients receiving concomitant enalapril and lithium and were reversible upon discontinuation of both drugs. It is recommended that serum lithium levels be monitored frequently if enalapril is administered concomitantly with lithium.

Hydrochlorothiazide: When administered concurrently the following drugs may interact with thiazide diuretics:

Alcohol, barbiturates, or narcotics—potentiation of orthostatic hypotension may occur.

Antidiabetic drugs (oral agents and insulin)—dosage adjustment of the antidiabetic drug may be required.

Other antihypertensive drugs—additive effect or potentiation.

Cholestyramine and colestipol resins—Cholestyramine and colestipol resins bind the hydrochlorothiazide and reduce its absorption from the gastrointestinal tract by up to 85 and 43 percent, respectively. Thiazides may be administered two to four hours before the resin when the two drugs are used concomitantly.

Corticosteroids, ACTH—intensified electrolyte depletion, particularly hypokalemia.

Pressor amines (e.g., norepinephrine)—possible decreased response to pressor amines but not sufficient to preclude their use.

Skeletal muscle relaxants, nondepolarizing (e.g., tubocurarine)—possible increased responsiveness to the muscle relaxant.

Lithium—should not generally be given with diuretics. Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity. Refer to the package insert for lithium preparations before use of such preparations with VASERETIC.

Non-steroidal Anti-inflammatory Drugs—In some patients, the administration of a non-steroidal anti-inflammatory agent can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing and thiazide diuretics. Therefore, when VASERETIC and non-steroidal anti-inflammatory agents are used concomitantly, the patient should be observed closely to determine if the desired effect of the diuretic is obtained.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Enalapril in combination with hydrochlorothiazide was not mutagenic in the Ames microbial mutagen test with or without metabolic activation. Enalapril-hydrochlorothiazide did not produce DNA single strand breaks in an *in vitro* alkaline elution assay in rat hepatocytes or chromosomal aberrations in an *in vivo* mouse

10 mg

25 mg

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bone marrow assay

Enalapril Maleate: There was no evidence of a tumorigenic effect when enalapril was administered for 106 weeks to rats at doses up to 90 mg/kg/day (150 times* the maximum daily human dose). Enalapril has also been administered for 94 weeks to male and female mice at doses up to 90 and 180 mg/kg/day, respectively, (150 and 300 times* the maximum daily dose for humans) and showed no evidence of carcinogenicity.

Neither enalapril maleate nor the active diacid was mutagenic in the Ames microbial mutagen test with or without metabolic activation. Enalapril was also negative in the following genotoxicity studies: rec-assay, reverse mutation assay with *E. coli*, sister chromatid exchange with cultured mammalian cells, and the micronucleus test with mice, as well as in an *in vivo* cytogenic study using mouse bone marrow.

There were no adverse effects on reproductive performance in male and female rats treated with 10 to 90 mg/kg/day of enalapril.

Hydrochlorothiazide: Two-year feeding studies in mice and rats conducted under the auspices of the National Toxicology Program (NTP) uncovered no evidence of a carcinogenic potential of hydrochlorothiazide in female mice (at doses of up to approximately 600 mg/kg/day) or in male and female rats (at doses of up to approximately 100 mg/kg/day). The NTP, however, found equivocal evidence for hepatocarcinogenicity in male mice.

Hydrochlorothiazide was not genotoxic *in vitro* in the Ames mutagenicity assay of *Salmonella typhimurium* strains TA 98, TA 100, TA 1535, TA 1537, and TA 1538 and in the Chinese Hamster Ovary (CHO) test for chromosomal aberrations, or *in vivo* in assays using mouse germinal cell chromosomes, Chinese hamster bone marrow chromosomes, and the *Drosophila* sex-linked recessive lethal trait gene. Positive test results were obtained only in the *in vitro* CHO Sister Chromatid Exchange (clastogenicity) and in the Mouse Lymphoma Cell (mutagenicity) assays, using concentrations of hydrochlorothiazide from 43 to 1300 µg/mL, and in the *Aspergillus nidulans* non-disjunction assay at an unspecified concentration.

Hydrochlorothiazide had no adverse effects on the fertility of mice and rats of either sex in studies wherein these species were exposed, via their diet, to doses of up to 100 and 4 mg/kg, respectively, prior to conception and throughout gestation.

Pregnancy, Pregnancy Categories C (first trimester) *and D* (second and third trimesters). See WARNINGS, *Pregnancy, Enalapril Maleate, Fetal/Neonatal Morbidity and Mortality.*

Nursing Mothers: Enalapril and enalaprilat are detected in human milk in trace amounts. Thiazides do appear in human milk. Because of the potential for serious reactions in nursing infants from either drug, a decision should be made whether to discontinue nursing or to discontinue VASERETIC, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: VASERETIC has been evaluated for safety in more than 1500 patients, including over 300 patients treated for one year or more. In clinical trials with VASERETIC no adverse experiences peculiar to this combination drug have been observed. Adverse experiences that have occurred, have been limited to those that have been previously reported with enalapril or hydrochlorothiazide.

The most frequent clinical adverse experiences in controlled trials were: dizziness (8.6 percent), headache (5.5 percent), fatigue (3.9 percent) and cough (3.5 percent). Adverse experiences occurring in greater than two percent of patients treated with VASERETIC in controlled clinical trials were: muscle cramps (2.7 percent), nausea (2.5 percent), asthenia (2.4 percent), orthostatic effects (2.3 percent), impotence (2.2 percent), and diarrhea (2.1 percent).

Clinical adverse experiences occurring in 0.5 to 2.0 percent of patients in controlled trials included: *Body As A Whole:* Syncope, chest pain, abdominal pain. *Cardiovascular:* Orthostatic hypotension, palpitation, tachycardia. *Digestive:* Vomiting, dyspepsia, constipation, flatulence, dry mouth. *Nervous/Psychiatric:* Insomnia, nervousness, paresthesia, somnolence, vertigo. *Skin:* Pruritus, rash. *Other:* Dyspnea, gout, back pain, arthralgia, diaphoresis, decreased libido, tinnitus, urinary tract infection.

Angioedema: Angioedema has been reported in patients receiving VASERETIC (0.6 percent). Angioedema associated with laryngeal edema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis and/or larynx occurs, treatment with VASERETIC should be discontinued and appropriate therapy instituted immediately. (See WARNINGS.)

Hypotension: In clinical trials, adverse effects relating to hypotension occurred as follows: hypotension (0.9 percent), orthostatic hypotension (1.5 percent), other orthostatic effects (2.3 percent). In addition syncope occurred in 1.3 percent of patients. (See WARNINGS.)

Cough: See PRECAUTIONS, *Cough.*

Clinical Laboratory Test Findings, Serum Electrolytes: See PRECAUTIONS.

Creatinine, Blood Urea Nitrogen: In controlled clinical trials minor increases in blood urea nitrogen and serum creatinine, reversible upon discontinuation of therapy, were observed in about 0.6 percent of patients with essential hypertension treated with VASERETIC. More marked increases have been reported in other enalapril experience. Increases are more likely to occur in patients with renal artery stenosis. (See PRECAUTIONS.)

Serum Uric Acid, Glucose, Magnesium, and Calcium: See PRECAUTIONS.

Hemoglobin and Hematocrit: Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.3 g percent and 1.0 vol percent, respectively) occur frequently in hypertensive patients treated with VASERETIC but are rarely of clinical importance unless another cause of anemia coexists. In clinical trials, less than 0.1 percent of patients discontinued therapy due to anemia.

Liver Function Tests: Rarely, elevations of liver enzymes and/or serum bilirubin have occurred.

Other adverse reactions that have been reported with the individual components are listed below and, within each category, are in order of decreasing severity.

Enalapril Maleate—Enalapril has been evaluated for safety in more than 10,000 patients. In clinical trials adverse reactions which occurred with enalapril were also seen with VASERETIC. However, since enalapril has been marketed, the following adverse reactions have been reported: *Body As A Whole:* Anaphylactoid reactions (see PRECAUTIONS, *Hemodialysis Patients*); *Cardiovascular:* Cardiac arrest, myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high risk patients (see WARNINGS, *Hypotension*), pulmonary embolism and infarction; pulmonary edema, rhythm disturbances including atrial tachycardia and bradycardia; atrial fibrillation, hypotension; angina pectoris. *Digestive:* Ileus, pancreatitis, hepatic failure, hepatitis (hepatocellular [proven on rechallenge] or cholestatic jaundice), melena, anorexia, glossitis, stomatitis, dry mouth. *Hematologic:* Rare cases of neutropenia, thrombocytopenia and bone marrow depression, a few cases of hemolysis in patients with G-6-PD deficiency have been reported in which a causal relationship to enalapril cannot be excluded; *Nervous System/Psychiatric:* Depression, confusion, ataxia, peripheral neuropathy (e.g., paresthesia, dysesthesia); *Urogenital:* Renal failure, oliguria, renal dysfunction (see PRECAUTIONS), flank pain, gynecomastia; *Respiratory:* Pulmonary infiltrates, bronchospasm, pneumonia, bronchitis, rhinorrhea, sore throat and hoarseness, asthma, upper respiratory infection. *Skin:* Exfoliative dermatitis, toxic epidermal necrolysis, Stevens-Johnson syndrome, herpes zoster, erythema multiforme, urticaria, alopecia, flushing, photosensitivity. *Special Senses:* Blurred vision, taste alteration, anosmia, conjunctivitis, dry eyes, tearing.

Miscellaneous: A symptom complex has been reported which may include a positive ANA, an elevated erythrocyte sedimentation rate, arthralgia/arthritis, myalgia, fever, serositis, vasculitis, leukocytosis, eosinophilia, photosensitivity, rash and other dermatologic manifestations.

Fetal/Neonatal Morbidity and Mortality: See WARNINGS, *Pregnancy, Enalapril Maleate, Fetal/Neonatal Morbidity and Mortality.*

Hydrochlorothiazide—Body as a Whole: Weakness. *Digestive:* Pancreatitis, jaundice (intrahepatic cholestatic jaundice), sialadenitis, cramping, gastric irritation, anorexia. *Hematologic:* Aplastic anemia, agranulocytosis, leukopenia, hemolytic anemia, thrombocytopenia; *Hypersensitivity:* Purpura, photosensitivity, urticaria, necrotizing angiitis (vasculitis and cutaneous vasculitis), fever, respiratory distress including pneumonitis and pulmonary edema, anaphylactic reactions. *Musculoskeletal:* Muscle spasm. *Nervous System/Psychiatric:* Restlessness. *Renal:* Renal failure, renal dysfunction, interstitial nephritis (see WARNINGS). *Skin:* Erythema multiforme including Stevens-Johnson syndrome, exfoliative dermatitis including toxic epidermal necrolysis, alopecia; *Special Senses:* Transient blurred vision, xanthopsia.

* Based on patient weight of 50 kg.

For more detailed information, consult your DuPont Pharma Representative or see Prescribing Information.

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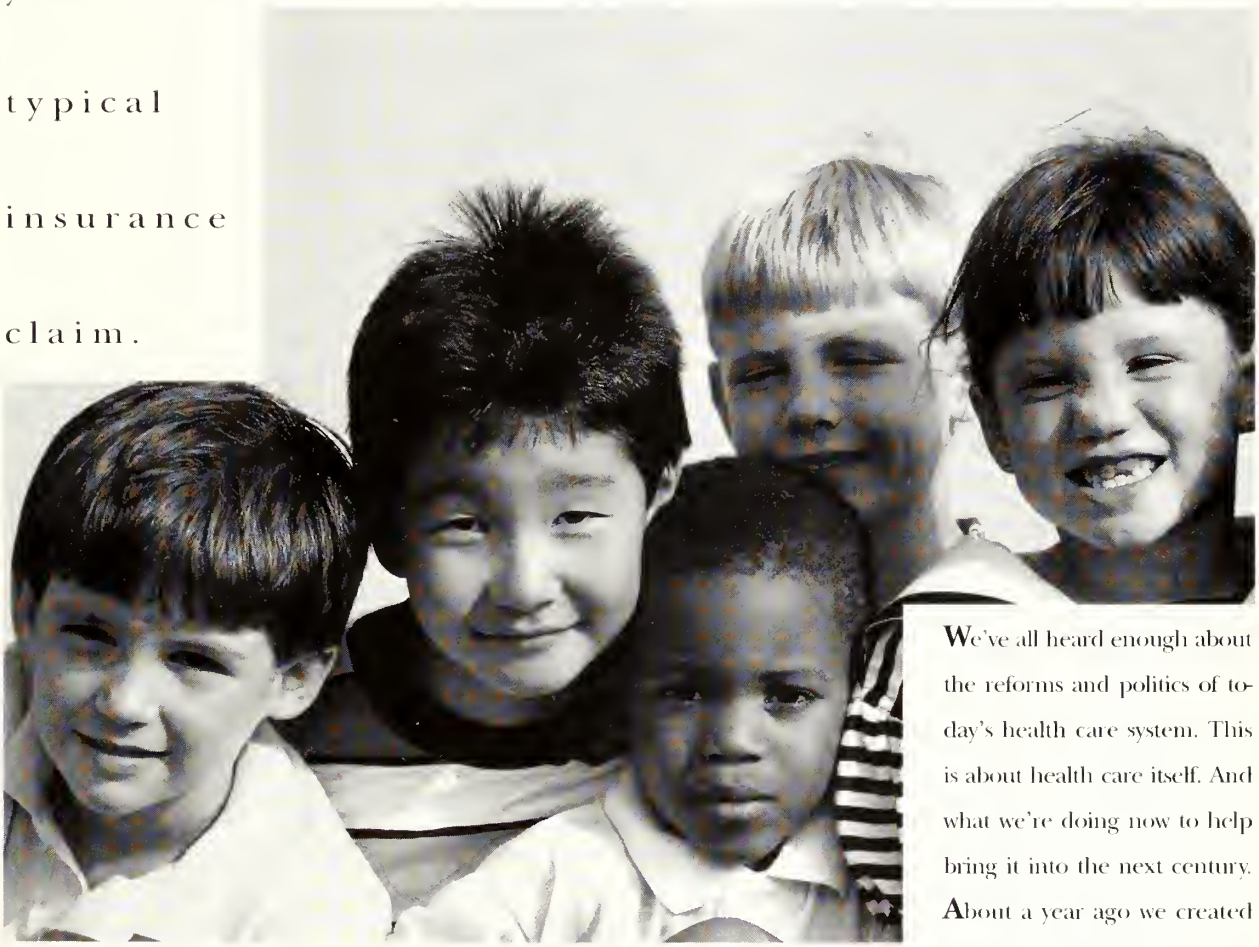

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The Swallowing Center Co-Directors

Tom R. DeMeester, M.D., professor and chairman, Department of Surgery at the University of Southern California School of Medicine, earned his medical degree from the University of Michigan, Ann Arbor, and received his surgical training at The Johns Hopkins Hospital in Baltimore. After a tour of military duty, Dr. DeMeester joined the faculty of the University of Chicago as Chief of Thoracic Surgery, a position he held for 10 years. He then served as Chairman of Surgery at Creighton University School of Medicine in Omaha, Nebraska. Dr. DeMeester joined USC in 1990.

Cedric G. Bremner, M.D., professor of Clinical Surgery and director of Clinical Research at USC, received his medical training at the University of the Witwatersrand in Johannesburg, South Africa, and spent five years at the Royal Postgraduate Medical School and the Hammersmith Hospital in London doing postgraduate studies. He also did his F.R.C.S. in England and Edinburgh, Scotland before returning to Johannesburg and becoming a staff member of the University Medical School. He spent a year at the Mayo Clinic and in 1979 was promoted to full professor of the University of Johannesburg. He joined USC in 1993.

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Warnings: Verapamil should be avoided in patients with severe LV dysfunction (eg, ejection fraction < 30%) or moderate to severe symptoms of cardiac failure and in patients with any degree of ventricular dysfunction if they are receiving a beta-blocker. Control milder heart failure with optimum digitalization and/or diuretics before Calan SR is used. Verapamil may occasionally produce hypotension. Elevations of liver enzymes have been reported. Several cases have been demonstrated to be produced by verapamil. Periodic monitoring of liver function in patients on verapamil is prudent. Some patients with paroxysmal and/or chronic atrial flutter/fibrillation and an accessory AV pathway (eg, WPW or LGL syndromes) have developed an increased antegrade conduction across the accessory pathway bypassing the AV node, producing a very rapid ventricular response or ventricular fibrillation after receiving I.V. verapamil (or digitalis). Because of this risk, oral verapamil is contraindicated in such patients. AV block may occur (2nd- and 3rd-degree, 0.8%). Development of marked 1st-degree block or progression to 2nd- or 3rd-degree block requires reduction in dosage or, rarely, discontinuation and institution of appropriate therapy. Sinus bradycardia, 2nd-degree AV block, sinus arrest, pulmonary edema and/or severe hypotension were seen in some critically ill patients with hypertrophic cardiomyopathy who were treated with verapamil.

Precautions: Verapamil should be given cautiously to patients with impaired hepatic function (in severe dysfunction use about 30% of the normal dose) or impaired renal function, and patients should be monitored for abnormal prolongation of the PR interval or other signs of overdosage. Verapamil may decrease neuromuscular transmission in patients with Duchenne's muscular dystrophy and may prolong recovery from the neuromuscular blocking agent vecuronium. It may be necessary to decrease verapamil dosage in patients with attenuated neuromuscular transmission. Combined therapy with beta-adrenergic blockers and verapamil may result in additive negative effects on heart rate, atrioventricular conduction and/or cardiac contractility; there have been reports of excessive bradycardia and AV block, including complete heart block. The risks of such combined therapy may outweigh the benefits. The combination should be used only with caution and close monitoring. Decreased metoprolol and propranolol clearance may occur when either drug is administered concomitantly with verapamil. A variable effect has been seen with combined use of etenolol. Chronic verapamil treatment can increase serum digoxin levels by 50% to 75% during the first week of therapy, which can result in digitalis toxicity. In patients with hepatic cirrhosis, verapamil may reduce total body clearance and extrarenal clearance of digitoxin. The digoxin dose should be reduced when verapamil is given, and the patient carefully monitored. Verapamil will usually have an additive effect in patients receiving blood-pressure-lowering agents. Disopyramide should not be given within 48 hours before or 24 hours after verapamil administration. Concomitant use of flecainide and verapamil may have additive effects on myocardial contractility, AV conduction, and repolarization. Combined verapamil and quinidine therapy in patients with hypertrophic cardiomyopathy should be avoided, since significant hypotension may result. Concomitant use of lithium and verapamil may result in an increased sensitivity to lithium (neurotoxicity), with either no change or an increase in serum lithium levels; however, it may also result in a lowering of serum lithium levels. Patients receiving both drugs must be monitored carefully. Verapamil may increase carbamazepine concentrations during combined use. Rifampin may reduce verapamil bioavailability. Phenobarbital may increase verapamil clearance. Verapamil may increase serum levels of cyclosporin. Verapamil may inhibit the clearance and increase the plasma levels of theophylline. Concomitant use of inhalation anesthetics and calcium antagonists needs careful titration to avoid excessive cardiovascular depression. Verapamil may potentiate the activity of neuromuscular blocking agents (curare-like and depolarizing); dosage reduction may be required. There was no evidence of a carcinogenic potential of verapamil administered to rats for 2 years. A study in rats did not suggest a tumorigenic potential, and verapamil was not mutagenic in the Ames test. Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy, labor, and delivery only if clearly needed. Verapamil is excreted in breast milk; therefore, nursing should be discontinued during verapamil use.

Adverse Reactions: Constipation (7.3%), dizziness (3.3%), nausea (2.7%), hypotension (2.5%), headache (2.2%), edema (1.9%), CHF, pulmonary edema (1.8%), fatigue (1.7%), dyspnea (1.4%), bradycardia: HR < 50/min (1.4%), AV block: total 1°,2°,3° (1.2%), 2° and 3° (0.8%), rash (1.2%), flushing (0.6%), elevated liver enzymes, reversible non-obstructive paralytic ileus. The following reactions, reported in 1.0% or less of patients, occurred under conditions where a causal relationship is uncertain: angina pectoris, atrioventricular dissociation, chest pain, claudication, myocardial infarction, palpitations, purpura (vasculitis), syncope, diarrhea, dry mouth, gastrointestinal distress, gingival hyperplasia, ecchymosis or bruising, cerebrovascular accident, confusion, equilibrium disorders, insomnia, muscle cramps, paresthesia, psychotic symptoms, shakiness, somnolence, arthralgia and rash, exanthema, hair loss, hyperkeratosis, macules, sweating, urticaria, Stevens-Johnson syndrome, erythema multiforme, blurred vision, gynecomastia, galactorrhea/hyperprolactinemia, increased urination, spotty menstruation, impotence.

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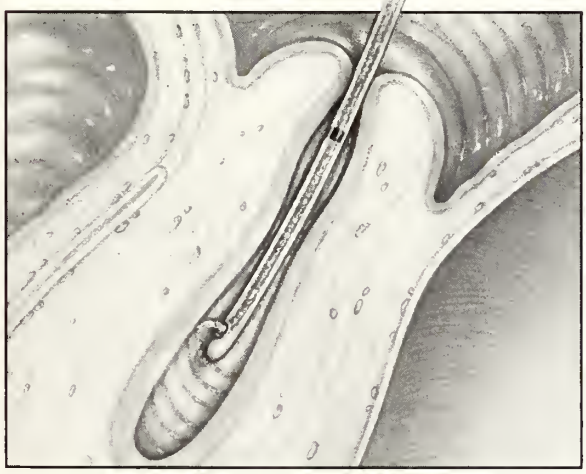

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November 18-21—**15th Annual Conference on Patient Education: Informing the Patient; Reforming the System.** American Academy of Family Physicians at Wyndam Paradise Valley Resort, Scottsdale. Thurs-Sun. Contact: Health Education Department, (800) 274-2237.

November 19—**Fifth Annual Update on Arthritis.** University of Arizona College of Medicine at Westin La Paloma Resort, Tucson. Fri. Contact: U of A.

November 19-20—**Molecular Biology: Applications in Clinical Medicine.** Mayo Clinic-Scottsdale at the Orange Tree Golf and Country Club, Scottsdale. Fri-Sat. Contact: Mayo Clinic-Scottsdale.

CONTACT INFORMATION

ArMA—Contact: Arizona Medical Association, 810 W Bethany Home Rd, Phoenix, AZ 85013. (602) 246-8901.

Mayo Clinic-Scottsdale—Contact: Postgraduate Courses, Mayo Clinic-Scottsdale, (602) 301-7447.

U of A—Contact: University of Arizona College of Medicine, Arizona Health Sciences Center, Tucson, AZ 85724. (602) 626-7832.

CALIFORNIA, HAWAII, AND NEVADA

This listing of continuing education programs in California, Hawaii, and Nevada is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Karen Williams, Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690; or phone (415) 882-5183. For more information on accreditation or certification, please write to the above address.

ALLERGY/IMMUNOLOGY

January 23-27—**Western Society of Allergy & Immunology: 32nd Annual Scientific Session.** Western Society of Allergy & Immunology at Ritz-Carlton, Mauna Lani, Island of Hawaii. Sun-Thurs. Contact: Rehecca Smith, PO Box 82268, Portland, OR 97282. (503) 774-3105.

March 19—**Immunologic Controversies Facing the Private Practitioner.** California Medical Association's Western Scientific Assembly at Disneyland Hotel, Anaheim. Sat. 3.5 hrs. Contact: Arlene Sirott, (415) 882-3384.

ANESTHESIOLOGY

November 19-20—**3rd Annual Pain Management.** UCD at Silverado Country Club, Napa. Fri-Sat. Contact: UCD.

January 16-22—**Hawaiian Seminar on Clinical Anesthesia.** California Society of Anesthesiologists at Westin Maui, Kaanapali Beach. Sun-Sat. 21 hrs. $425. Contact: CSA, 1065 E Hillsdale Blvd, Ste 410, Foster City 94404. (800) 345-3691.

January 28-30—**32nd Clinical Conference in Pediatric Anesthesiology.** Children's Hospital Los Angeles at Disneyland Hotel, Anaheim. Fri-Sun. 15 hrs. Contact: Children's Hospital, PO Box 54700, Los Angeles 90054. (213) 669-2262.

February 23-27—**The Practicing Physician's Approach to the Difficult Headache Patient.** Dannemiller Memorial Educational Foundation at Marriott's Rancho Las Palmas Resort and Country Club, Rancho Mirage. Wed-Sun. Contact: Seymour Diamond, 5252 N Western Ave, Chicago, Il 60625. (312) 907-6226.

March 19-20—**Case Conference in Anesthesia.** California Society of Anesthesiologists at Dana Point Resort. Sat-Sun. 9 hrs. $185. Contact: CSA, 1065 E Hillsdale Blvd, Ste 410, Foster City 94404. (800) 345-3691.

April 2-3—**22nd Obstetric/Anesthesia Conference.** Ohio State Department of Anesthesiology at Sheraton Waikiki Hotel, Honolulu, Hawaii. Sat-Sun. 20 hrs. $610. Contact: Arlene Rogers, 410 W 10th Ave, Columbus, OH 43210. (614) 293-8487.

April 5-8—**Hawaiian Pain Conference.** Ohio State University Department of Anesthesiology at Grand Hyatt, Wailea, Maui. Tues-Fri. 16 hrs. $610. Contact: Arlene Rogers, Ohio State University, 410 W 10th Ave, Columbus, OH 43210. (614) 293-8153.

April 9-10—**39th PGA Conference.** Los Angeles County Society of Anesthesiologists at UCLA Faculty Center. Sat-Sun. 13 hrs. Contact: LACSA, PO Box 90999, Long Beach 90809-0999. (213) 597-2661.

CARDIOLOGY

April 11-13—**4th Annual Symposium on Coronary Stenting.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Mon-Wed. 20 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

DERMATOLOGY

January 21-23—**Cutaneous Malignancies: 1994 Skin Cancer Update.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Fri-Sun. 17 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

January 21-23—**Practical Dermatology and Dermatologic Office Procedures for the Primary Care Physician.** UCSD at Hyatt Regency, La Jolla. Fri-Sun. 20 hrs. $495. Contact: Jacqueline Shiller, (619) 223-2997.

March 18—**Current Issues in Dermatology.** California Medical Association's Western Scientific Assembly at Disneyland Hotel, Anaheim. Fri. 3 hrs. Contact: Arlene Sirott, (415) 882-3384.

EMERGENCY MEDICINE

December 5-10—**14th Annual Conference: Current Concepts in Emergency Care.** American College of Emergency Physicians Washington Chapter at Maui Intercontinental Resort, Maui, Hawaii. Sun-Fri. 20 hrs. Contact: Kailani World Travel, 4192 Meridian Ave, Box 9751, Bellingham, WA 98227. (800) 544-9269 or (206) 671-1800.

January 10-14—**Emergency Medicine Symposia I.** UCSD at La Jolla Marriott. Mon-Fri. 32 hrs. $495. Contact: UCSD.

January 19-22—**The California Trauma Conference.** UCSF at San Francisco. Wed-Sat. Contact: UCSF.

January 22-29—**Update: Controversies in Emergency and Primary Care.** UCSD at The Royal Waikoloan, Kohala Coast, Hawaii. 1 wk. Contact: Edith Bookstein, PO Box 2586, La Jolla 92038. (619) 454-3212.

February 26-March 5—**Cardiac Emergencies.** UCSD at Royal Lahaina Resort, Maui, Hawaii. 1 wk. 21 hrs. $450. Contact: Edith Bookstein, PO Box 2586, La Jolla 92038. (619) 454-3212.

March 6-11—**14th Annual Mammoth Mountain Emergency Medicine Ski Conference.** American College of Emergency Physicians at Mammoth Lakes. Sun-Fri. 18 hrs. $395. Contact: Daniel Abbott, PO Box 52-B, Newport Beach 92662. (714) 650-4156.

FAMILY PRACTICE/PRIMARY CARE

December 2-4—**Obstetrics and Gynecology Conference.** University of Nebraska at Bally's Las Vegas. Thurs-Sat. $275. Contact: University of Nebraska Medical Center, 600 S 42nd St, Omaha, NE 68198-5651. (402) 559-4152 or (800) 642-1095.

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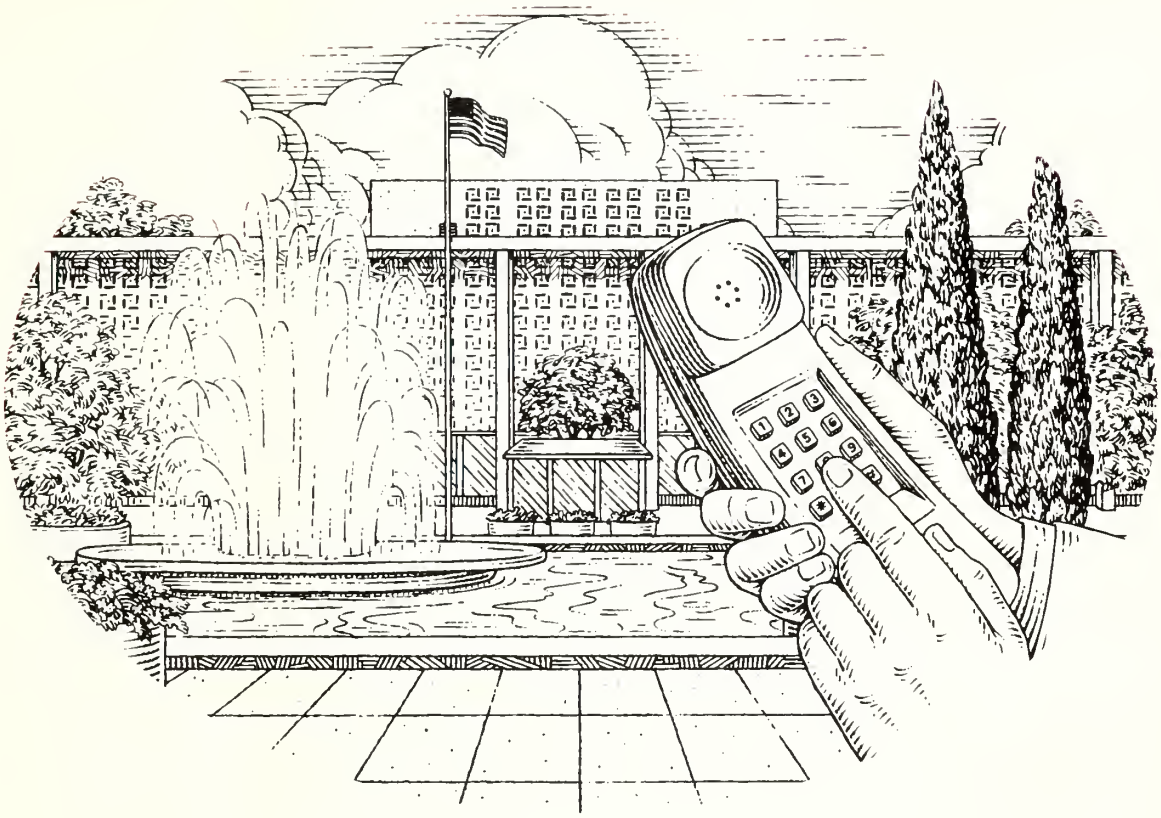

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AASH

American Association for the Study of Headache

The American Association For The Study Of Headache

Winter Postgraduate Course

Update on Headache: A Comprehensive Course in Mechanisms and Management

Marriott's Camelback Inn Resort and Spa

Scottsdale, Arizona

Friday, January 21- Sunday, January 23, 1994

The American Association for the Study of Headache is proud to offer this intensive and comprehensive program designed to provide the practicing physician, dentist and allied health professional an updated and "hands on" experience in the management of headache.

Who should attend?

This conference is designed for family practitioners, internists, neurologists, anesthesiologists, dentists, physical therapists, psychologists, nurses, and other health professionals who treat headaches.

The goals of the Winter Postgraduate Course are to:

- review advances in the pathophysiology of pain and headache
- discuss the latest advances in migraine therapy
- examine the relationship between migraine theory and therapy
- explore the psychological aspects of headache management
- discuss the clinical and therapeutic aspects of cluster headache
- recognize the differences and similarities of tension type and migraine headaches
- address the differential diagnosis of head pain
- discuss the medical/legal issues as they relate to patients with head pain

Clip and Send to:

The American Association
for the Study of Headache
Winter Postgraduate Course
875 Kings Highway, Suite 200
Woodbury, N.J. 08096-3172

I am interested in attending The American Association for the Study of Headache's Winter Postgraduate course in Scottsdale, Arizona. Please send further information.

Please Print or Type:

Name: _____

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Country: _____

Zip/Postal Code: _____

Future AASH Meetings
36th Annual Scientific Meeting
June 24- 26, 1994 Chicago, Illinois
Call For Papers Deadline February 1, 1994

WJM

FACULTY

Course Co-Directors

Herbert G. Markley, M.D
Headache Center, Department of Neurology
Medical Center of Central Massachusetts
Worcester, Massachusetts

Paul K. Winner, D.O.
Palm Beach Headache Center
West Palm Beach, Florida

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Stamford, Connecticut

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Philadelphia, Pennsylvania

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Mayo Medical School Clinic
Rochester, Minnesota

James R. Couch, M.D., Ph.D.
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Oklahoma City, Oklahoma

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Buckingham, Doolittle & Burroughs
Akron, Ohio

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Neil H. Raskin, M.D
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San Francisco, California

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Michigan Head • Pain and Neurological Institute
Ann Arbor, Michigan

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The New England Center for Headache
Stamford, Connecticut

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Comprehensive Headache Center
Philadelphia, Pennsylvania

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Cleveland Clinic Foundation
Cleveland, Ohio

Seymour Solomon, M.D
Montefiore Headache Unit
Bronx, New York

K.M.A. Welch, M.D
Department of Neurology
Henry Ford Hospital
Detroit, Michigan

Paul K. Winner, D.O.
Palm Beach Headache Center
West Palm Beach, Florida

The American Association for the Study of Headache
875 Kings Highway, Suite 200
Woodbury, N.J. 08096-3172
Phone: (609) 845-1720
Fax (609) 384-5811

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January 21-23—**Practical Dermatology and Dermatologic Office Procedures for the Primary Care Physician.** UCSD at Hyatt Regency, La Jolla. Fri-Sun. 20 hrs. $495. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

February 4-5—**Pediatric Dermatology for the Primary Care Physician.** UCSF and Stanford at Sheraton Palace Hotel, San Francisco. Fri-Sat. 10.5 hrs. $275. Contact: UCSF.

February 5-12—**5th Kaiser Permanente National Conference on Musculoskeletal Medicine.** Kaiser Permanente at Hyatt Regency, Kauai, Hawaii. 1 week. 29 hrs. $400. Contact: Ferdy Massimino, MD, 200 Muir Rd, Martinez 94553. (510) 372-1457.

February 18-20—**Office Gynecology for the Primary Care Physician.** SDSU at Hyatt Islandia, San Diego. Fri-Sun. 20 hrs. $450. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

March 18—**Cancer Detection and Follow-Up for the Primary Care Physician.** California Medical Association's Western Scientific Assembly at Disneyland Hotel, Anaheim. Fri. 4 hrs. Contact: Arlene Sirott, (415) 882-3384.

March 19—**Emergencies in Primary Care.** California Medical Association's Western Scientific Assembly at Disneyland Hotel, Anaheim. Sat. 4 hrs. Contact: Arlene Sirott, (415) 882-3384.

March 19—**Psychiatric Emergencies in Primary Care: A How To Primer.** California Medical Association's Western Scientific Assembly at Disneyland Hotel, Anaheim. Sat. 3.5 hrs. Contact: Arlene Sirott, (415) 882-3384.

March 20—**Outpatient Procedures for the Primary Care Physician.** California Medical Association's Western Scientific Assembly at Disneyland Hotel, Anaheim. Sun. 3.5 hrs. Contact: Arlene Sirott, (415) 882-3384.

March 20—**Urology for the Primary Care Physician.** California Medical Association's Western Scientific Assembly at Disneyland Hotel, Anaheim. Sat. 5.5 hrs. Contact: Arlene Sirott, (415) 882-3384.

March 23-25—**Annual Review in Family Medicine: Controversies and Challenges in Primary Care.** UCSF at Hotel Nikko, San Francisco. Wed-Fri. 16 hrs. $300. Contact: UCSF.

March 28-31—**Primary Care in Paradise.** Scripps Clinic and Research Foundation at Princeville Resort, Island of Kauai, Hawaii. Mon-Thurs. 16 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Blvd, La Jolla 92037. (619) 554-8556.

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690. (415) 541-0900.

CPMC: California Pacific Medical Center
Contact: Continuing Education, California Pacific Medical Center, PO Box 7999, San Francisco 94120. (415) 923-3441.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Herbert M. Thomas, MD, MPH, Director of CME, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th St, Los Angeles 90059. (213) 603-3183.

LLU: Loma Linda University
Contact: James J. Couperus, MD, Associate Dean for Educational Affairs, Loma Linda University School of Medicine, Loma Linda 92350.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Medical School Office Building, Suite X-365, Stanford 94305-6114 (415) 723-5594.

UCD: University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, 2701 Stockton Blvd, Sacramento 95817. (916) 734-5390.

UCI: University of California, Irvine
Contact: Melvin I. Marks, MD, Director, Memorial/UCI Center for Health Education, Long Beach Memorial Medical Center, 2801 Atlantic Ave, PO Box 1428, Long Beach, California 90801-1428. (213) 595-3811.

UCLA: University of California, Los Angeles Extension
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, PO Box 24902, UCLA, Los Angeles 90024. (310) 825-8423.

UCSD: University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (619) 534-3940.

UCSF: University of California, San Francisco
Contact: Janet Johnson, Administrative Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 476-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 1975 Zonal Ave, KAM314, Los Angeles 90033. (800) 872-1119.

1993-1994—**HIV Primary Care Mini-Residency.** UCSD at Owen Clinic, San Diego. Ongoing. 30 hrs. Contact: UCSD.

GERIATRICS

January 18-22—**11th Annual Intensive Course in Geriatric Medicine and Board Review.** UCLA at Beverly Hilton Hotel, Beverly Hills. Tues-Sat. 44 hrs. $675. Contact: UCLA.

March 20—**Long Term Care Update.** California Medical Association's Western Scientific Assembly at Disneyland Hotel, Anaheim. Sun. 3.5 hrs. Contact: Arlene Sirott, (415) 882-3384.

1993-1994—**Mini-residency in Geriatrics.** UCSD at Multi Purpose Facility, San Diego. Ongoing. 40-80 hrs. $195. Contact: UCSD.

1993-1994—**The GGG/Alzheimer's Family Center: Sharing the Caring—Training Series on Dementia.** UCSD. Ongoing. 4 hrs. $25. Contact: UCSD.

INFECTIOUS DISEASES

December 13-15—**Clinical Care of the AIDS Patient.** UCSF at Sheraton Palace Hotel, San Francisco. Tues-Thurs. 15 hrs. $295. Contact: UCSF.

February 4-5—**12th Annual Infectious Disease Conference.** UCD at Hilton Hotel, Sacramento. Fri-Sat. 11 hrs. $160. Contact: UCD.

INTERNAL MEDICINE

January 19-22—**Advanced Nephrology: Nephrology for the Consultant.** UCSD at Hyatt Islandia Hotel, San Diego. Wed-Sat. 25 hrs. $500. Contact: UCSD.

February 3-5—**17th Annual Neurology for the Non-Neurologists.** UCSD at Pan Pacific Hotel, San Diego. Thurs-Sat. 21 hrs. $450. Contact: Edith Bookstein, PO Box 2586, La Jolla 92038. (619) 454-3212.

February 5—**New Advances in Inflammatory Bowel Disease.** Scripps Clinic and Research Foundation at Green Hospital Amphitheater. Sat. 7 hrs. $140. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

February 17-19—**Recent Advances in Neurology.** UCSF at Sheraton Palace Hotel, San Francisco. Thurs-Sat. 15 hrs. $355. Contact: UCSF.

February 26-27—**Endoscopy 1994.** Southern California Society for Gastrointestinal Endoscopy at Century Plaza Hotel, Los Angeles. Sat-Sun. Contact: Joyce M. Fried, 10833 Le Conte Ave, Los Angeles 90024-1722. (310) 374-9708.

March 4—**20th Annual Diabetes Symposium.** UCD at Sheraton Sunrise Hotel, Sacramento. Fri. 6 hrs. $130. Contact: UCD.

March 18-24—**Internal Medicine: 1994.** Sharp Memorial Hospital at Hotel del Coronado, San Diego. Fri-Thurs. 54 hrs. $695. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

OB/GYN

November 20—**Infertility Update VII.** Scripps Clinic and Research Foundation, La Jolla. Sat. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

December 2-3—**Controversies in Women's Health.** UCSF at Hotel Nikko, San Francisco. Thurs-Fri. Contact: UCSF.

December 2-4—**Obstetrics and Gynecology Conference.** University of Nebraska at Bally's Las Vegas. Thurs-Sat. $275. Contact: University of Nebraska Medical Center, 600 S 42nd St, Omaha, NE 68198-5651. (402) 559-4152 or (800) 642-1095.

January 16-18—**Ambulatory Obstetrics and Gynecology.** UCD at Hyatt Regency Lake Tahoe, Incline Village, Nevada. Sun-Tues. 14.5 hrs. $300-$375. Contact: UCD.

March 19—**Health Care Issues for Women Over 40.** California Medical Association's Western Scientific Assembly at Disneyland Hotel, Anaheim. Sat. 3.5 hrs. Contact: Arlene Sirott, (415) 882-3384.

April 20-24—**Pacific Coast Fertility Society Annual Scientific Program and Postgraduate Course.** Pacific Coast Fertility Society at Stouffer Esmeralda Resort, Indian Wells. Wed-Sun. 17 hrs. Contact: Director, Continuing Medical Education, 15731 Imperial Hwy, Ste 427, La Mirada 90638-2510. (310) 947-7068.

OCCUPATIONAL/ENVIRONMENTAL

January 31-February 4—**Occupational and Environmental Medicine.** UCSF at Miyako Hotel, San Francisco. Mon-Fri. Contact: UCSF.

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CONTINUING MEDICAL EDUCATION

(Continued from Page 547)

March 19—**Practical Aspects of Occupational Medicine.** California Medical Association's Western Scientific Assembly at Disneyland Hotel, Anaheim. Sat. 4 hrs. Contact: Arlene Sirott, (415) 882-3384.

ONCOLOGY

November 20—**Breast Cancer: New Directions.** UCSF at Sheraton Palace Hotel, San Francisco. Sat. Contact: UCSF.

December 5—**Tumors of the Female Genital Tract.** California Tumor Tissue Registry at Ritz-Carlton Hotel, San Francisco. Sat. 8 hrs. $55. Contact: California Tumor Tissue Registry, c/o Loma Linda University, 11021 Campus Ave, AH 335, Loma Linda 92354. (909) 824-4788.

January 28-30—**46th Annual Midwinter Oncology Conference.** Los Angeles Radiological Society at Century Plaza Hotel, Los Angeles. Fri-Sun. 16.5 hrs. $450. Contact: LARS, PO Box 91215, Los Angeles 90009-1215. (310) 827-9078 or (800) 527-7013.

February 21-23—**Clinical Hematology and Oncology: 1994.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Mon-Wed. 18 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

OPHTHALMOLOGY

December 9-11—**Cornea and Excimer Update Symposium and Workshop.** UCSF at Ana Hotel and University, San Francisco. Thurs-Sat. 13 hrs. Contact: UCSF.

March 20—**Ophthalmologist-Gatekeeper Interactions: Managed Eye Care.** California Medical Association's Western Scientific Assembly at Disneyland Hotel, Anaheim. Sun. 3.5 hrs. Contact: Arlene Sirott, (415) 882-3384.

ORTHOPEDICS

December 1-4—**Cost Effective Back Care.** American Back Society at San Francisco Hilton & Towers. Wed-Sat. Contact: Aubrey Swartz, 2647 E 14th St, Ste 401, Oakland 94601. (510) 536-9929.

December 3-5—**Review and Update for Practicing Orthopedic Surgeons.** American Academy of Orthopedic Surgeons at Sheraton Palace Hotel, San Francisco. Fri-Sun. Contact: AAOS, 6300 N River Rd, Rosemont, IL 60018-4262. (800) 346-2207.

December 8-12—**American Back Society Meeting.** American Back Society at Hyatt Regency Embarcadero, San Francisco. Wed-Sun. Contact: ABS, 2647 E 14th St, Ste 401, Oakland 94601. (510) 536-9929.

January 20-23—**Reconstruction of the Adult Hip: A Comprehensive Course.** American Academy of Orthopedic Surgeons at Hyatt Regency Maui, Lahaina, Hawaii. Thurs-Sun. Contact: AAOS, 6300 N River Rd, Rosemont, IL 60018-4262. (708) 823-7186.

January 23-26—**Fracture Management.** UCD at Resort at Squaw Creek, Squaw Valley. Sun-Wed. 15 hrs. $495. Contact: UCD.

January 27-30—**Spring Meeting of the Northern California Chapter of the Western Orthopedic Association** at Inn at Squaw Creek, Olympic Valley. Thurs-Sun. Contact: Iola Beckley, (707) 538-5548.

March 20—**Musculoskeletal Trauma in Children and Adolescents.** California Medical Association's Western Scientific Assembly at Disneyland Hotel, Anaheim. Sun. 3.5 hrs. Contact: Arlene Sirott, (415) 882-3384.

OTOLARYNGOLOGY

November 14-19 and December 5-10—**Temporal Bone Dissection Course.** House Ear Institute. Sun-Fri. 53 hrs. $875-$1,100. Contact: Antonio De la Cruz, 2100 W Third St, Los Angeles 90057. (213) 483-4431 ext. 7079.

March 18—**Pediatric Otolaryngology: What Gatekeepers Need to Know.** California Medical Association's Western Scientific Assembly at Disneyland Hotel, Anaheim. Fri. 4 hrs. Contact: Arlene Sirott, (415) 882-3384.

April 6-8—**Temporomandibular Joint Update.** UCD at Silverado Resort, Napa. Wed-Fri. 12 hrs. $300. Contact: UCD.

PATHOLOGY

March 18—**Skin Cancer: A Clinical and Histopathologic Update.** California Medical Association's Western Scientific Assembly at Disneyland Hotel, Anaheim. Fri. 3 hrs. Contact: Arlene Sirott, (415) 882-3384.

April 16—**New Treatments in Chronic Liver Disease.** Scripps Clinic and Research Foundation at La Jolla. Fri. 6 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Blvd, La Jolla 92037. (619) 554-8556.

PEDIATRICS

December 4-5—**Stabilization and Management of the Critically Ill Child.** UCSF at San Francisco. Sat-Sun. 9 hrs. $220. Contact: UCSF.

January 24-28—**San Diego Conference on Responding to Child Maltreatment.** Children's Hospital San Diego at Town and Country Hotel, San Diego. Mon-Fri. $390. Contact: Center for Child Protection, 8001 Frost St, San Diego 92123. (619) 395-4950.

February 21-23—**Pediatrics Update 1994.** San Diego State University at Hyatt Islandia, San Diego. Mon-Wed. 20 hrs. $450. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2297.

March 19—**Pediatrics Emergencies.** California Medical Association's Western Scientific Assembly at Disneyland Hotel, Anaheim. Sat. 4 hrs. Contact: Arlene Sirott, (415) 882-3384.

PSYCHIATRY

November 18-20—**Addiction Medicine: State of the Art 1993.** California Society of Addiction Medicine at Four Seasons Hotel, Newport Beach. Thurs-Sat. 19 hrs. $350. Contact: CSAM, 3803 Broadway, Oakland 94611. (510) 428-9091.

January 23-28—**20th Annual Midwinter Program in Continuing Medical Education for Psychiatrists.** UCD at Hyatt Regency Lake Tahoe, Incline Village, Nevada. Sun-Fri. 25 hrs. $395. Contact: UCD.

February 26—**1994 Sleep Medicine Update.** Scripps Clinic and Research Foundation at La Jolla. Sat. 7 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

March 5, 6, 19, 20—**Introductory Workshop in Clinical Hypnosis for Physicians, Dentists and Psychologists.** San Francisco Academy of Hypnosis at Alta Bates Hospital, Berkeley. Sat-Sun. 28 hrs. $375. Contact: San Francisco Academy of Hypnosis, Verna Carter, 29 Pinto Ave, San Francisco 94132. (415) 239-4104.

RADIOLOGY

January 17-19—**Neuroradiology Update.** Stanford University Medical Center at Ritz-Carlton, Laguna Niguel. Mon-Wed. 17.5 hrs. $450. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

January 20-23—**Breast Imaging Update.** Stanford University Medical Center at Ritz-Carlton Hotel, Laguna Niguel. Thurs-Sun. 16 hrs. $450. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

February 14-18—**Magnetic Resonance Imaging.** UCSD at Hotel del Coronado, San Diego. Mon-Fri. 30 hrs. $425. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

February 21-25—**Contemporary Diagnostic Imaging.** Stanford University Medical Center at Ritz-Carlton Resort Hotel, Kapalua, Hawaii. Mon-Fri. 20.5 hrs. $550. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925.

March 7-10—**Magnetic Resonance Imaging.** UCSD at Hotel del Coronado, San Diego. Mon-Thurs. 30 hrs. $625. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

March 19—**Dilemmas in Women's Imaging.** California Medical Association's Western Scientific Assembly at Disneyland Hotel, Anaheim. Sat. 4 hrs. Contact: Arlene Sirott, (415) 882-3384.

March 21-26—**Musculoskeletal and Neuro MRI.** UCSD at La Costa Resort and Health Spa, Carlsbad. Mon-Sat. 19.5 hrs. $550. Contact: UCSD.

April 3-8—**14th Annual Residents Radiology Review Course.** UCSD at Hotel Del Coronado, San Diego. Sun-Fri. 41 hrs. $450. Contact: UCSD.

April 9—**Interventional Radiology.** UCSD at Hotel Del Coronado, San Diego. Sat. 8 hrs. $135. Contact: UCSD.

1993-1994—**Fellowship in Interventional Radiology for Radiologists.** UCSD Medical Center. Ongoing. 40 hrs. $700. Contact: UCSD.

1993-1994—**Visiting Fellowship in Magnetic Resonance Imaging.** UCSD at MR Institute, San Diego. Ongoing. 40 hrs. $1,200. Contact: UCSD.

1993-1994—**Visiting Fellowship for Physicians and Sonographers in Duplex Ultrasound: Focus on Carotid and Deep Venous Thrombosis.** Ongoing. 30 hrs. $600. Contact: UCSD.

SURGERY

January 14-15—**What's New in General Surgery.** UCD at Hyatt Regency Hotel, Sacramento. Fri-Sat. 15 hrs. $285. Contact: UCD.

(Continued on Page 550)

OCCUPATIONAL & ENVIRONMENTAL MEDICINE

Presented by:
Division of
Occupational & Environmental Medicine
University of California, San Francisco
Program fee: $725
40 AMA Category 1 credit hours
Contact:
UCSF, Postgraduate Programs
Department of Medicine
1383 Ninth Avenue
San Francisco, California 94122
(415) 476-5208

COURSE SERIES
January 31-February 4, 1994
San Francisco, California

New One-Week Session Format

The five one-week series is designed to present the basic clinical and administrative aspects of occupational and environmental medicine.

Individual sessions can also be used as updates on many aspects of the practice of OEM.

JANUARY'S PROGRAM HIGHLIGHTS:

- Clinical Toxicology
- Industrial Hygiene
- Occupational Diseases
- Occupational Injuries
- Ergonomics
- Occupational Cardiology

University of Colorado's CME IN THE ROCKIES

Sponsored by the University of Colorado School of Medicine

For further information contact the Office of Continuing Medical Education at (800) 882-9153 or (303) 372-9050.

Eligible for Category I AMA credit hours.

UNIVERSITY OF COLORADO · CONTINUING MEDICAL EDUCATION

1993-94 WINTER SERIES HIGHLIGHTS

DECEMBER 1993

1. Practical Issues in Infectious Disease: Bugs & Drugs in the '90s
   December 10-11, 1993 Denver, CO

JANUARY 1994

2. Reconstructive Surgery of the Hip and Knee
   January 22-29, 1994 Steamboat Springs, CO
3. 5th Annual Geriatrics Overview/Board Review
   January 23-29, 1994 Breckenridge, CO
4. Contemporary Management of Unstable Coronary Syndromes
   January 27-29, 1994 Breckenridge, CO

FEBRUARY 1994

5. Renal & Liver Transplantation 1994: Current Issues in Management
   February 3-6, 1994 Breckenridge, CO
6. 9th Annual Rocky Mountain HIV Disease Conference
   February 4-5, 1994 Denver, CO
7. Horizons in Surgery
   February 26-March 3, 1994 Breckenridge, CO
8. Colorado Review of Anesthesia
   February 26-March 4, 1994 Vail, CO

MARCH 1994

9. Colorado Conference on Decision-Based Family Practice
   March 20-23, 1994 Denver, CO

APRIL 1994

10. OB/GYN Update
    April 29-May 1, 1994 Denver, CO

JUNE 1994

11. 40th Annual Family Practice Review
    June 12-18, 1994 Estes Park, CO
12. 7th World Conference on Lung Cancer
    June 26-July 1, 1994 Colorado Springs, CO

JULY 1994

13. 30th Annual Internal Medicine Program
    July 10-15, 1994 Estes Park, CO
14. 21st Annual Renal Disease Program
    July 25-29, 1994 Aspen, CO
15. 3rd Annual Medical Ethics Conference
    July 29-31, 1994 Aspen, CO
16. Management of Pediatric Diabetes in the 1990s
    July 31-August 3, 1994 Keystone, CO

AUGUST 1994

17. 18th Annual Dynamic Psychotherapy Program
    August 1-5, 1994 Aspen, CO
18. 37th Annual Pediatric Program
    August 7-11, 1994 Aspen, CO
19. 19th Annual Primary Musculoskeletal Care Program
    August 7-12, 1994 Breckenridge, CO
20. 4th Annual Musculoskeletal Infection Meeting
    August 17-20, 1994 Snowmass Village, CO

SEPTEMBER 1994

21. The Changing Colors of Perinatal Outreach Education
    September 15-17, 1994 Durango, CO

American Society of Addiction Medicine

1994 CERTIFICATION AND RECERTIFICATION EXAM

for Physicians in the diagnosis and treatment of alcoholism and other drug dependencies

WHEN: SATURDAY, DECEMBER 3, 1994
APPLICATION DEADLINE: JANUARY 10, 1994 CALL FOR SITE LOCATION

1994 MEDICAL REVIEW OFFICER TRAINING

MARCH 11-13, 1994 MARINA DEL REY, CA
AUGUST 26-28, 1994 ARLINGTON, VA

FOR FURTHER INFORMATION, PLEASE CONTACT ASAM AT (202) 244-8948 OR FAX (202) 537-7252

CONTINUING MEDICAL EDUCATION

(Continued from Page 548)

March 24-25—**9th Annual Course in Colon and Rectal Surgery.** USC at Ritz-Carlton Huntington Hotel, Pasadena. Thurs-Fri. Contact: Donna Bowker, 1975 Zonal Ave, KAM 307, Los Angeles 90033. (213) 342-2555.

March 24-26—**6th Annual Symposium on Aesthetic Surgery of the Face.** UCSF at San Francisco. Thurs-Sat. Contact: UCSF.

GENERAL/MULTIDISCIPLINARY

January 7-9—**7th Annual Medical Office Laboratory Conference.** SDSU at Red Lion Hotel, San Diego. Fri-Sun. 20 hrs. $425. Contact: Nancy Geiser, (619) 594-6255.

January 27-30—**Medicine Meets Virtual Reality II: Interactive Technology & Healthcare: Visionary Applications for Simulation, Visualization and Robotics.** UCSD at San Diego Marriott & Marina. Thurs-Sun. 21 hrs. $390. Contact: UCSD.

February 6-11—**26th Annual CME/Ski Meeting.** Nevada Academy of Family Physicians at Harvey's Resort, Lake Tahoe. Sun-Fri. 39 hrs. Contact: Debi Bradley, PO Box 7471, Reno, NV 89510. (702) 826-5100.

February 12-13—**Clinical Applications of Vestibular Science.** UCLA. Sat-Sun. $350. Contact: Marjorie Harris, 15-50 Rehabilitation Center, UCLA 90024. (310) 825-5131.

February 14-18—**5th Annual Physician Heal Thyself.** UCSD at Palm Springs Hilton. Mon-Fri. 16 hrs. $395. Contact: UCSD.

March 20—**Risk Issues in Cost Contained Care.** California Medical Association's Western Scientific Assembly at Disneyland Hotel, Anaheim. Sun. 3 hrs. Contact: Arlene Sirott, (415) 882-3384.

HOME STUDY/SELF ASSESSMENT

Audio-Digest Foundation. California Medical Association. Contact: Audio-Digest Foundation, 1577 E Chevy Chase, Glendale 91206. (213) 245-8505.

COLORADO

This listing of continuing medical education programs in Colorado is compiled by the Denver Medical Society. To list CME programs here, please send information at least two months in advance to: Mr Robert L. Kennedy, Denver Medical Society, 1850 Williams Street, Denver, CO 80218; or telephone (303) 377-1850.

Brochures, course information, and registration forms are available from the contact person or organization.

December 18—**Computers in Medicine.** Rose Medical Center at Hotel L'Ostello, Vail. Sat. Repeated weekly through April 23, 1994, at either Hotel L'Ostello, Vail, or Hotel Wildwood, Snowmass Village. Contact: Bernard Karshmer, (800) 525-5810.

January 27-29—**Contemporary Management of Unstable Coronary Syndromes.** Department of Veterans Affairs at Beaver Run Resort, Breckenridge. Thurs-Sat. Contact: Karen Babcock, (303) 393-2826.

January 29-February 5—**Internal Medicine Conference.** Rose Medical Center at Radisson Resort, Vail. Sat-Sat. Contact: Bernard Karshmer, (800) 525-5810.

February 5-12—**General Surgery Conference.** Rose Medical Center at Radisson Resort, Vail. Sat-Sat. Contact: Bernard Karshmer, (800) 525-5810.

February 12-19—**Emergency Medicine Conference.** Rose Medical Center at Radisson Resort, Vail. Sat-Sat. Contact: Bernard Karshmer, (800) 525-5810.

February 12-19—**Psychiatry Conference.** Rose Medical Center at Radisson Resort, Vail. Sat-Sat. Contact: Bernard Karshmer, (800) 525-5810.

February 19-26—**Neurology Conference.** Rose Medical Center at the Antlers Hotel, Vail. Sat-Sat. Contact: Bernard Karshmer, (800) 525-5810.

February 19-26—**Obstetrics and Gynecology Conference.** Rose Medical Center at Radisson Resort, Vail. Sat-Sat. Contact: Bernard Karshmer, (800) 525-5810.

February 26-March 5—**Pediatrics Conference.** Rose Medical Center at Radisson Resort, Vail. Sat-Sat. Contact: Bernard Karshmer, (800) 525-5810.

February 26-March 5—**Infectious Disease Conference.** Rose Medical Center at the Antlers Hotel, Vail. Sat-Sat. Contact: Bernard Karshmer, (800) 525-5810.

March 5-12—**Primary Care Conference.** Rose Medical Center at Radisson Resort, Vail. Sat-Sat. Contact: Bernard Karshmer, (800) 525-5810.

March 5-12—**Minding the Body/Mending the Mind.** Rose Medical Center at the Antlers Hotel, Vail. Sat-Sat. Contact: Bernard Karshmer, (800) 525-5810.

March 6-11—**14th Annual Keystone ENT Conference.** University of Nebraska Medical Center at Keystone Resort, Keystone. Sun-Fri. Contact: U of Nebraska Continuing Education Center, (402) 559-4152.

March 12-19—**Sports Medicine Conference.** Rose Medical Center at Radisson Resort, Vail. Sat-Sat. Contact: Bernard Karshmer, (800) 525-5810.

March 12-19—**Urology Conference.** Rose Medical Center at Radisson Resort, Vail. Sat-Sat. Contact: Bernard Karshmer, (800) 525-5810.

March 19-26—**Cancer Treatment Conference.** Rose Medical Center at the Antlers Hotel, Vail. Sat-Sat. Contact: Bernard Karshmer, (800) 525-5810.

Tuesday Noon Conferences—**Various Topics in Medicine.** Lutheran Medical Center, Wheat Ridge. Contact: Jean A. Kline, (303) 425-2951.

Every Second Wednesday of the Month—**Cardiovascular Education Series.** St Anthony Hospitals at St Anthony Hospital, Denver. Contact: Rose Powell, (303) 629-3678.

Every Friday (except 4th Friday of month)—**Various Topics in Contemporary Medicine (Midday CME Series).** St Anthony Hospitals at St Anthony Hospital, Denver. Contact: Rose Powell, (303) 629-3678.

First Wednesday of Each Month—**Various Topics in Neurology.** Sponsored by the Colorado Society of Clinical Neurologists. Contact: Colorado Society of Neurologists, (303) 449-3566.

CONTACT INFORMATION

U of Colo—Contact: University of Colorado School of Medicine, Office of Continuing Medical Education, 4200 E 9th Ave, Denver, CO. (303) 270-5195 or (800) 882-9153; FAX (303) 270-6761.

IDAHO

July 28-30—**Idaho Medical Association—Annual Meeting.** Sun Valley. Wed-Fri. Contact: IMA, 305 W. Jefferson, PO Box 2668, Boise 83701. (208) 344-7888.

NEW MEXICO

Information, requests for accreditation, and items to be listed should be sent to the chair of the CME Committee, New Mexico Medical Society, 7770 Jefferson, Suite 400, Albuquerque, NM 87109, at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 828-0237.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

November 20—**Alcoholism and Substance Abuse.** UNM Nursing and Pharmacy College, Albuquerque. Sat. Contact: Psychiatric Medical Association, (505) 291-5375.

December 2—**New Mexico Society of Internal Medicine Practice Management Seminar: "Surviving Change."** The Marshall Building, Albuquerque. Thurs. Contact: Elsa Hall, New Mexico Medical Society, 7770 Jefferson NE, Suite 400, Albuquerque 87109. (505) 828-0237.

December 2-4—**New Mexico Chapter, American College of Physicians, Annual Meeting.** Albuquerque Marriott. Thurs-Sat. Contact: UNM SOM.

CONTACT INFORMATION

UNM SOM—University of New Mexico School of Medicine, Office of CME, PO Box 713, Albuquerque 87131. (505) 277-3942.

(Continued on Page 552)

CALIFORNIA MEDICAL ASSOCIATION'S
WESTERN SCIENTIFIC ASSEMBLY
AND 123RD ANNUAL SESSION

Western Scientific Assembly and Annual Session

March 17-23, 1994
Disneyland Hotel, Anaheim

Mark your March calendar for CMA's premier educational event! The 1994 Western Scientific Assembly continues CMA's commitment to offering an outstanding educational event featuring dozens of practical multispecialty courses in clinical medicine and showcasing many of California's finest educators.

This year's Assembly offers exceptional value! Enjoy quality, convenience, and affordability at the largest multispecialty meeting on the West Coast.

- 43 courses spanning the breadth of medical and surgical specialties
- 157 hours of CME credit approved by CMA, AAFP, ACEP, and BRN

This year's rich variety of courses showcases front-line issues in primary care of interest to all physicians. Topics include:

- Cancer Detection, Treatment and Follow-up
- Women's Health Issues
- Pediatrics
- Ambulatory Surgery
- Emergency Medicine
- Pain Management
- Public Health Issues
- Neurological Updates
- Managed Care Topics
- Procedural Workshops
- Practice Management Seminars

FREE ANNUAL SESSION EVENTS

Open to all attendees.

- Golden Apple Award and Reception honoring Sherman Mellinkoff, MD of UCLA
- Distinguished Speaker, Robert E. Rakel, MD on "The Future of General Medicine"
- A Critical Look At the Washington Scene
- Medical Progress: A Miracle at Risk
- CMA House of Delegates
- CMA-HMSS, YPS, and Alliance

EXHIBIT HALL

The Exhibit Hall will feature the products and services you need: pharmaceuticals, medical equipment and testing systems, computer systems, insurance, and many more health care related exhibits. For information regarding exhibiting, contact Robert Shapiro at (415) 882-5119.

Send this coupon to receive a copy of the complete Advance Program or call (415) 882-3384.

Please send me the Advance Program for the CMA's 1994 Annual Session and Western Scientific Assembly.

Name _____

Address _____

City, State, Zip _____

MAIL this form to: California Medical Association, ATTN: Coordinator, Western Scientific Assembly, P.O. Box 7690, San Francisco, CA 94120-7690.

WJM

(Continued from Page 550)

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. Accredited institutions wishing to list AMA Category 1 CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, UT 84102; or phone (801) 355-7477. For information on CME accreditation, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution.

December 5-9—**Intensive Neuroradiology.** Marriott Hotel, Salt Lake City. Sun-Thurs. Contact: UUSM.

January 19-22—**Midwinter Conference on Chest Disease.** Cliff Lodge, Snowbird. Wed-Sat. Contact: ITS.

January 29-February 5—**Richard Lende Winter Neurosurgery Conference.** Cliff Lodge, Snowbird. Sat-Sat. Contact: UANS.

February 7-11—**Surgical Pathology.** Yarrow Hotel, Park City. Mon-Fri. Contact: UUSM.

February 14-18—**Update in Clinical Microbiology and Immunology.** Yarrow Hotel, Park City. Mon-Fri. Contact: UUSM.

February 17-19—**UOS Annual Winter Ski Meeting.** Yarrow Hotel, Park City. Thurs-Sat. Contact: UOS.

February 17-24—**37th Anesthesiology Update: Anesthesia and the Nervous System.** Snowbird Cliff Lodge. 1 week. Contact: UUSM.

February 23-27—**Physical Medicine and Rehabilitation Update.** Prospector Square Conference Center, Park City. Wed-Sun. Contact: UUSM.

February 27-March 2—**35th Annual OB/GYN Update.** Yarrow Hotel, Park City. Sun-Wed. Contact: UUSM.

March 2-5—**Surgical Oncology Update.** Yarrow Hotel, Park City. Wed-Sat. Contact: UUSM.

March 6-11—**Advances in Internal Medicine.** Cottonwood Center, Snowbird. Sun-Fri. Contact: UUSM.

March 8-12—**Microsurgery Workshop.** University Park Hotel, Salt Lake City. Thurs-Sat. Contact: UUSM.

March 11-12—**Western Intermountain Neurological.** University Park Hotel, Salt Lake City. Fri-Sat. Contact: UUSM.

MEDICAL GRAND ROUNDS

Weekly—Internal Medicine Grand Rounds, Psychiatry Grand Rounds, OB/GYN Grand Rounds, Pediatric Grand Rounds. Contact: UUSM, Office of CME, (801) 581-8664.

SPONSORS OF COURSES—ABBREVIATIONS

CH:	Castleview Hospital, 300 N Hospital Dr, Price 84501. (801) 637-4800.
CS:	Charter Summit Hospital, 175 W 7200 South, Midvale 84047. (801) 561-8181.
DM:	Dixie Medical Center, 544 S 400 East, St George 84770. (801) 634-4000.
ETS:	Emergency Training Services, 777 N 390 East, American Fork 84003. (801) 763-3555.
FHP:	FHP of Utah, 35 W Broadway, Salt Lake City 84101. (801) 355-1234.
ITS:	Intermountain Thoracic Society, 1616 S 11th East, Salt Lake City 84105. (801) 484-4456.
LDSH	LDS Hospital, 8th Ave and "C" St, Salt Lake City 84143. (801) 321-1100.
LRH:	Logan Regional Hospital, 1400 N 5th East, Logan 84321. (801) 752-2050.
MDH:	McKay-Dee Hospital Center, 3939 Harrison Blvd, Ogden 84409. (801) 625-2694.
MVH	Mountain View Hospital, 1000 E Highway 6, Payson 84651. (801) 465-9201.
OSS:	Ogden Surgical-Medical Society, PO Box 9311, Ogden 84409.
PCMC:	Primary Children's Medical Center, 100 N Medical Dr, Salt Lake City 84113. (801) 588-2000.
PVH	Pioneer Valley Hospital, 3460 S 4155 West, West Valley City 84120. (801) 968-9061.
UANS	Utah Association of Neurological Surgeons, 24 South 1100 East, Suite 302, Salt Lake City 84102. (801) 531-7806.
UMIA	Utah Medical Insurance Association, 540 E 500 South, Salt Lake City 84102. (801) 531-0375.
UMA:	Utah Medical Association, 540 E Fifth South, Salt Lake City 84102. (801) 355-7477.
UOS:	Utah Ophthalmological Society, 540 E 500 South, Salt Lake City 84102. (801) 355-7477.
USH:	Utah State Hospital, PO Box 270, Provo 84603-0270. (801) 373-4400.
UUSM:	University of Utah School of Medicine, Office of Continuing Medical Education, 50 N Medical Dr, Salt Lake City 84132. (801) 581-8664.
VAMC:	Veterans Administration Medical Center, 500 Foothill Dr, Salt Lake City 84148. (801) 582-1565.

WASHINGTON

The listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here, please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 1100, Seattle, WA 98121; or phone (206) 441-9762 or (800) 552-0612.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

November 18-19—**Diabetes Update.** Thurs-Fri. Contact: U/W.

November 19—**Advances in Therapeutics for the Clinician.** Renton. Fri. Contact: VMC, (206) 228-3440.

December 2-4—**American College of Physicians.** Seattle. Thurs-Sat. Contact: U/W.

December 3-4—**Pain Update '93: Integrating Pain Management in the Rehabilitation Process.** Bellevue. Fri-Sat. Contact: U/W.

December 9—**Scientists in the Courtroom: The Role of the Expert Witness.** Seattle. Thurs. Contact: Northwest Center for Occupational Health and Safety, (206) 543-1069.

December 9-10—**Advanced Cardiac Life Support.** Tacoma. Thurs-Fri. Contact: PCMS CME.

December 9-12—**9th Infectious Disease Conference.** Everett. Tues-Sat. Contact: PNMEH, (206) 258-6322.

December 10-11—**Mental Health Update.** Fri-Sat. Contact: U/W.

December 10-11—**Regional Musculoskeletal Conference.** Seattle. Fri-Sat. Contact: U/W.

January 20—**Law and Medicine Symposium.** Tacoma. Thurs. Contact: PCMS CME.

January 22—**Orthopedic Update.** Seattle. Sat. Contact: Children's Hospital, (206) 526-2501.

February 12-16—**WAPA Board Certification Review Course.** Seattle. Sat-Wed. Contact: Washington Academy of Physician Assistants, (206) 441-9762.

February 25—**Review of HIV Infections.** Tacoma. Fri. Contact: PCMS CME.

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104. (206) 223-5953.

PCMS CME—Contact: Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 223-6898.

WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Suite 1100, Seattle, WA 98121. (206) 441-9762.

WYOMING

June 9-11—**Wyoming Medical Society—Annual Meeting.** Jackson Lake Lodge, Moran. Thurs-Sat. Contact WMS, PO Drawer 4009, Cheyenne 82003-4009. (307) 635-2424. ◆

CONTINUING MEDICAL EDUCATION CALENDAR

The Southern Medical Association is accredited by the Accreditation Council for Continuing Medical Education to sponsor continuing medical education for physicians.

DECEMBER 3-4, 1993

SPA PSYCHIATRIC UPDATE
LOCATION: Birmingham, Alabama
SPECIALTY: Psychiatry
CME CREDIT: AMA Category I-5 hours
FEE: SMA/SPA Member-$100; Nonmember-$200; Nonphysician-$50

DECEMBER 3-5, 1993

BURN SEMINAR
LOCATION: Orlando, Florida
SPECIALTY: Burn Center Directors and Health Care Professionals
CME CREDIT: AMA Category I
FEE: All Participants $75

JANUARY 28-30, 1994

KNEE SYMPOSIUM
LOCATION: Orlando, Florida
SPECIALTY: Orthopaedics
CME CREDIT: AMA Category I-11 hours
FEE: SMA Member-$140; Nonmember-$290; Residents/Fellows-$30

JANUARY 29-FEBRUARY 5, 1994

PREVENTIVE MEDICINE
LOCATION: Tucson, Arizona
SPECIALTY: Primary Care
CME CREDIT: AMA Category I-39 hours
FEE: SMA Member-$475; Nonmember-$600; Nonphysician-$300

FEBRUARY 2-4, 1994

ENT UPDATE
LOCATION: St. Thomas, Virgin Islands
SPECIALTY: Otolaryngology
CME CREDIT: AMA Category I-12 hours
FEE: SMA Member-$475; Nonmember-$600; Nonphysician-$300

FEBRUARY 8-13, 1994

THORACIC & CARDIOVASCULAR SURGERY
LOCATION: Grand Cayman Islands
SPECIALTY: Thoracic & Cardiovascular Surgery
CME CREDIT: AMA Category I
FEE: SMA Member-$375; Nonmember-$500; Nonphysician-$250

FEBRUARY 11-13, 1994

THE ATHLETIC PATIENT
LOCATION: Fort Lauderdale, Florida
SPECIALTY: Sports Medicine, Primary Care, Orthopaedics, Internal Medicine
CME CREDIT: AMA Category I-14 hours; AAFP Prescribed-14 hours; AOA Category 2-A-14 hours
FEE: SMA Member-$375; Nonmember-$500; Nonphysician-$250

FEBRUARY 17-19, 1994

4TH ANNUAL UPDATE IN MAMMOGRAPHY
LOCATION: Aruba
SPECIALTY: Radiology
CME CREDIT: AMA Category I-15 hours
FEE: SMA Member-$395; Nonmember-$520; Nonphysician-$275

For more information, call Michelle Williamson, Southern Medical Association, 800-423-4992 or 205-945-1840—TODAY!

INSTRUCTIONS FOR AUTHORS

Manuscript Information

Manuscripts should be sent to the Editor, Linda Hawes Clever, MD, *The Western Journal of Medicine*, 221 Main Street, San Francisco, California 94105. Manuscripts must be original, not previously published, and not under consideration by another publication. If preliminary data were included in another presentation or publication, this should be noted in the cover letter and a copy of that publication should be included.

MANUSCRIPTS OF THESE LENGTHS WILL BE GIVEN PREFERENCE

- Articles: 2,000 words*
- Conferences and Reviews: 3,000 words*
- Alerts, Notices, and Case Reports: 1,500 words
- Lessons From the Practice: 1,000 words
- Letter to the Editor: 500 words

**These totals include references and the abstract but not tables.*

All manuscripts will be subject to peer review.

Letter of Transmittal

All authors must sign the letter of transmittal, with one author designated as correspondent and his or her name, address, and telephone number included.

The order of authorship is determined by the authors. All authors should meet the basic criteria for authorship (as stated below). Because order of authorship is assigned in different ways, its meaning cannot be inferred accurately unless it is stated by the authors. Authors may wish to add an explanation of the order of authorship in a footnote. In deciding on order, authors should be aware that many journals limit the number of authors listed in the table of contents and that the National Library of Medicine lists in MEDLINE only the first 10 authors.

A letter of transmittal, except for one accompanying a manuscript from US Government employees whose work was done as part of their official duties, must include a paragraph that transfers copyright: "In consideration for reviewing and editing my submission, the author(s) undersigned hereby transfers, assigns, or otherwise conveys all copyright ownership to *The Western Journal of Medicine*, in the event that such work is published by the journal."

The letter of transmittal must include a statement of author responsibility: "I have participated in the conception and design of this work and in the writing of the manuscript and take public responsibility for it. I have reviewed the final version of the manuscript and approve it for publication. I attest to the validity and legitimacy of data in the manuscript and agree to be named as the lead author or coauthor of the manuscript."

The letter of transmittal must include a statement of financial disclosure: "I warrant that I have no financial interest in the drugs, devices, or procedures described in the enclosed manuscript (except as disclosed herewith)."

Research or project support should be included as a footnote to the manuscript or in the accompanying cover letter.

Manuscripts concerned with experimental investigation on human subjects must include in the text a statement that all subjects gave their informed consent and that approval of the appropriate ethics committee was obtained.

Acknowledgments will be printed on a select basis—to acknowledge those who contributed to but were not involved in the writing or review of the paper. They should not include persons whose work on the manuscript was a part of their regular duties.

Preparation of Manuscripts

Everything, including references, tables, figure legends, and abstracts, **must be double-spaced.**

The original manuscript and two copies should be submitted on standard-sized heavy bond paper. Allow a margin of 2.5 to 4 cm (1 to 1.5 in) on both sides. Manuscripts transmitted by facsimile machine are not acceptable unless requested by the Editors.

All values should be in Système International (SI) units, with metric equivalents following in parentheses. Temperature readings should be given in Celsius. Use the generic name of drugs, with the salt or ester given when first used.

Figures (illustrations) should be submitted in triplicate in black and white, unmounted 12.7 × 17.8 cm (5 × 7 in) glossy prints, with the figure number, author's name, and top of the photo indicated with a label on the back. Patients (and relatives) have a right to anonymity in published clinical documentation. Details that might identify patients should be avoided unless essential for scientific purposes. Masking of the eye region in photographs of patients may be inadequate protection of anonymity. If identification of patients is unavoidable, informed consent should be obtained, and this should be clearly stated in the article. Changing data on patients should not be used as a way of securing anonymity. Figure legends, to be typed in sequence on the same page, should be in complete sentences. Any figures or tables previously published must be accompanied by a letter of permission to borrow from the copyright holder (the previous publisher). The permission of the authors should also be obtained. The Editors discourage the use of borrowed figures or tables.

Reprints

A form to order reprints will be sent to the author when the article is published.

References

All references should be cited in the text using superscript numbers and listed in their order of citation. They should be pertinent to the text and not simply a listing of the results of a computerized search. They should be in *WJM* style (see previous copy of journal).

All references should be medical, scientific, or scholarly publications. Others—newspapers, magazines, etc—should be kept to a minimum and included in the text.

For a complete guide to WJM *style for references, see the two-page Instructions for Authors in a previous issue.*

CHECKLIST

- Original manuscript and 2 copies
- **Everything** including tables and references double-spaced
- Illustrations, black and white glossy, identified with lead author's name—3 sets, plus figure legends that describe fully and in complete sentences what the figure depicts
- Letter of transmittal that includes release of copyright, statement of conflict of interest, and authorship responsibility, **signed by all authors**
- A 200-word abstract
- Title page that includes current affiliation of all authors and address **and telephone number** for corresponding author
- Permission-to-borrow letters for any previously published illustrations or tables
- All references numbered consecutively, double-spaced, in *WJM* style, and cited in text. No unpublished data or nonscientific publications listed in references (include in text)

Articles

Helicobacter pylori and Peptic Ulcer Disease

MARK FELDMAN, MD, *and* WALTER L. PETERSON, MD, *Dallas, Texas*

Medical therapy for duodenal or gastric ulcer disease has traditionally involved gastric acid antisecretory therapy for 4 to 8 weeks to promote initial healing and indefinitely to prevent recurrences of ulcer. The discovery of *Helicobacter pylori* in most patients with peptic ulcer disease has led to a change in this approach. Therapy designed to eradicate *H pylori* may facilitate ulcer healing with acid antisecretory agents and, more important, may greatly reduce the incidence of ulcer recurrence, obviating the need for maintenance antisecretory therapy. Regimens designed to eradicate *H pylori* are difficult to comply with, however, and are associated with adverse effects in some patients. In this article we review the diagnosis and treatment of *H pylori* infection in patients with peptic ulcer disease and make recommendations regarding the use of conventional ulcer therapies and therapies designed to eradicate *H pylori.*

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In this brief article we review some recent advances in our understanding of peptic ulcer disease, emphasizing the evolving role of *Helicobacter pylori*. *Helicobacter pylori* (formerly known as *Campylobacter pylori*) is a curved, motile, microaerophilic gram-negative rod that is found in the mucus layer overlying the epithelium of the gastric mucosa. It clusters around junctions between gastric cells without invading the epithelium.[1] Infected persons may also harbor *H pylori* in metaplastic and heterotopic gastric epithelium.[2]

In North America, more than 50% of asymptomatic persons older than 60 years show evidence of active or past *H pylori* infection.[3-5] Earlier and more frequent rates of infection are associated with race and ethnicity (African American and Hispanic), socioeconomic deprivation, and residence in custodial institutions.[6-8] In underdeveloped parts of the world, the prevalence of *H pylori* colonization of the gastric mucosa is nearly 80% by the age of 30.[9] Patients with active or inactive peptic ulcer disease (especially duodenal but also gastric) have *H pylori* infection more often than age-matched controls,[6,10] with a relative risk of around 2 or 3 to 1 (Table 1).*

The evidence for person-to-person transmission of *H pylori* is supported by familial clustering[11,12] and a higher-than-expected prevalence of the organism in residents of custodial institutions and nursing homes.[9,13] Person-to-person transmission can occur through endoscopic biopsy forceps.[14] Gastroenterologists have more than twice the expected prevalence of infection.[15] One study showed that the prevalence of infection was associated with the source of the drinking water, suggesting waterborne spread.[16] Although this may be an important factor in developing countries, where the water supply may be vulnerable to bacterial contamination, the organism has not yet been identified in water or food. A recent study showed that *H pylori* can often be cultured from the stool of infected persons, suggesting that fecal-oral transmission may occur.[17]

Virtually all who harbor *H pylori* in their antral mucosa have focal epithelial cell damage and inflammation in the lamina propria.[18,19] Evidence that *H pylori* may induce gastritis is supported by studies in animals[20,21] and humans.[22-25] *Helicobacter pylori* attaches tightly to gastric epithelial cells and forms a characteristic structure, called an "attachment pedestal," that appears to cause local cell damage.[26] Urease production seems to be important for colonization, perhaps because it protects *H pylori* from the bactericidal effect of acid[27] or because it enhances bacterial adherence.[28] Urease has also been shown to be cytotoxic to human gastric epithelial cells.[29] The microorganism also produces catalases, proteases, and phospholipases A_2 and C that cause damage to cell membranes and degrade gastric mucus. In addition, it produces a cytotoxin.[30] Finally, *H pylori* produces chemotactic factors for monocytes and neutrophils leading to influx of these cells and the release of inflammatory cytokines, eicosanoids, and reactive oxygen intermediates.[31-33]

Although some studies reported that chronic infection of *H pylori* is associated with an increase in gastric acid secretion,[34-36] most studies have been unable to find a convincing relationship between acid secretion and chronic *H*

*See also the editorial by J. I. Isenberg, MD, "Is Peptic Ulcer Disease an Infectious Disease?" on pages 616-618.

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TABLE 1.—*Gastric* Helicobacter pylori *on Biopsy Specimens in Case-Controlled Study**

Ulcer Type by Location	H pylori Cultured From Specimen: Ulcer Patients, %	Controls (n=26), %	Ratio (CI)
Gastric (n=36)			
Fundus	78	31	2.53 (1.39-4.62)
Antrum	69	27	2.58 (1.31-5.00)
Duodenal (n=33)			
Fundus	88	31	2.86 (1.58-5.16)
Antrum	91	27	3.38 (1.77-6.49)

CI = confidence interval

*From Cryer et al.[10]

pylori infection.[37-42] Hypochlorhydria may occur as a sequela of acute *H pylori* infection.[22,43] Early studies did not find a relationship between *H pylori* and serum gastrin concentrations.[38,39] Most recent studies, however, have reported increased serum gastrin concentrations in persons infected with *H pylori* and reductions in serum gastrin concentrations after *H pylori* eradication.[37,41,44] The exaggerated gastrin response in *H pylori* infection may be a consequence of antral gastritis per se, a direct effect of *H pylori* on antral G (gastrin) cells,[45] or a result of less somatostatin inhibition of antral G cells,[46] although this last mechanism has been challenged.[47]

The high incidence of *H pylori* infection in patients with peptic ulcer disease suggests a role for the organism in its pathogenesis. Further support for this concept comes from the lower relapse rates of peptic ulcer disease after the eradication of *H pylori* (discussed later). The most important argument against the role of *H pylori* in ulcer disease is the observation that most people with this organism never have an ulcer. In some third world countries where most people older than 30 years are infected with *H pylori* (80% in some areas of Africa), the prevalence of peptic ulcer disease is much lower than in the United States.[48] *Helicobacter pylori* appears to be a strong risk factor for ulcer development, but its presence is not sufficient to cause ulcers.

A hypothesis for the role of *H pylori* in the pathogenesis of duodenal ulcer disease has been suggested (Figure 1).[49] High gastric acid secretion, common in persons with duodenal ulcer, seems to be associated with gastric metaplasia in the duodenal bulb.[50] Thus, *H pylori*-infected patients who have gastric metaplasia in the duodenum as a consequence of acid hypersecretion are prone to duodenal colonization with *H pylori*, which subsequently may cause duodenitis by a mechanism similar to that described for *H pylori*-associated gastritis. Once *H pylori*-related gastritis (and possibly duodenitis) is established, the presence of acid or pepsin will enhance mucosal injury. Concomitant smoking, the use of nonsteroidal anti-inflammatory drugs, or other factors may act synergistically with *H pylori* to damage the gastroduodenal mucosa. This hypothesis does not explain how gastric metaplasia develops in the duodenal bulb of patients with duodenal ulcer who are not acid hypersecretors; in such patients gastric metaplasia may be congenital, or, alternatively, metaplasia may not even be required for duodenal ulcerogenesis. Moreover, this explanation implies that the acid hypersecretion present in many duodenal ulcer patients is not of itself sufficient to cause duodenal ulcers. Duodenal ulcers will likely recur in some of these patients even after *H pylori* has been eradicated, much as duodenal ulcers occur in other acid hypersecretory disorders unrelated to *H pylori*, such as the Zollinger-Ellison syndrome.

Diagnosis of *Helicobacter pylori* Infection

Helicobacter pylori can be histologically identified in a biopsy specimen using hematoxylin and eosin, Warthin-Starry silver, or Giemsa stains. Urease tests on biopsy material involve placing the specimen in a urea-containing solution or gel containing phenol red (a pH indicator). If *H pylori* is present, urea is hydrolyzed to release ammonia, increasing the pH in the solution or gel, and giving it a pink color. These tests are commercially available and can be read in two to three hours.[15,52] Culturing of *H pylori* from biopsy material is tedious, and results are not available for several days. Urea breath tests for *H pylori* require ingesting a solution containing urea labeled with carbon 13 or carbon 14. If *H pylori* is present in the stomach, [^{13}C]dioxide or [^{14}C]dioxide is split off by urease, absorbed, and expired in the breath. Sensitivities and specificities of breath tests are greater than 90%.[53,54] These breath tests are not yet commercially available. A serologic diagnosis is based on enzyme-linked immunosorbent assays, which have a reported sensitivity of 99% and a specificity of 100%.[55] Serologic testing, however, will not distinguish active infection from a previously treated and now inactive infection.

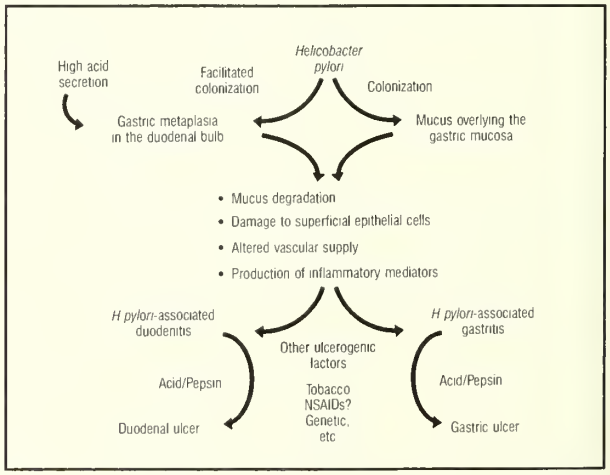

Figure 1.—The diagram illustrates the hypothesis linking *Helicobacter pylori*, high acid secretion, and gastric metaplasia in the duodenal bulb in the pathogenesis of duodenal and gastric ulcer disease (see text). (Reproduced with permission from Goldschmiedt and Peterson.[49]) NSAIDs = nonsteroidal anti-inflammatory drugs

Implications for Ulcer Therapy

Histamine H_2-receptor antagonists, antacids, and sucralfate do not kill *H pylori*. In vitro, however, sucralfate appears to counteract the mucolytic activity of the microorganism,[56] may inhibit *H pylori* adhesion and growth,[57] and may act as an ammonia scavenger and protect the gastric mucosa from ammonia-induced injury.[58] Proton pump inhibitors such as omeprazole may suppress *H pylori*[59] and, in combination with antibiotics and bismuth compounds, increase the eradication rates of *H pylori* (discussed later).

Trials using bismuth compounds or single antibiotic agents as monotherapy have shown unacceptably low rates of *H pylori* eradication and relatively high ulcer recurrence rates. "Triple therapy" regimens include the use of a bismuth compound, a nitroimidazole (metronidazole or tinidazole) and either tetracycline or amoxicillin.[60-63] The regimen we recommend is listed in Table 2.[64,65] Although triple-drug therapy will eradicate *H pylori* in 65% to 94% of patients,[63] it is associated with gastrointestinal intolerance leading to poor compliance in around 30% of patients, has the potential of serious side effects, and may induce bacterial resistance. Eradication failure, arbitrarily defined as the persistence of *H pylori* four weeks after therapy is completed,[62] may be more common in areas where giardiasis and amebiasis are endemic and where nitroimidazole-resistant strains of *H pylori* are prevalent. Once eradication failure is demonstrated, it may be useful to culture *H pylori* from biopsy material and to do in vitro antibiotic sensitivities before embarking on a second course of therapy.

Recent studies have focused on ways to eradicate *H pylori* with more tolerable therapeutic regimens. In one study, a combination of omeprazole and amoxicillin eradicated *H pylori* in 22 of 27 patients with duodenal ulcers.[66] But other investigators using the same drugs could not eradicate *H pylori* in patients with nonulcer dyspepsia or duodenal ulcers.[67] Other regimens combining omeprazole, colloidal bismuth subcitrate, and clarithromycin have been shown to eradicate *H pylori* in more than 50% of patients.[68] Shorter regimens (1 week) have been tried combining tinidazole and amoxicillin with or without bismuth compounds, with eradication rates as high as 62%.[64,69] In one study, the treatment of duodenal ulcers with omeprazole for four weeks plus bismuth, tetracycline, and metronidazole for one week eradicated *H pylori* in 95% of patients.[70]

Numerous studies have shown a substantial reduction in the relapse rate of duodenal ulcers in patients in whom *H pylori* was eradicated.[64,65,71-82] For example, a combination of amoxicillin, 750 mg three times a day, and metronidazole, 500 mg three times a day, given without bismuth for 12 days eradicated *H pylori* in 89% of patients compared with 2% eradication in patients treated with placebo (both groups received ranitidine hydrochloride). Ulcers recurred in 8% of patients during the year following amoxicillin-metronidazole therapy compared with an 86% recurrence rate in placebo-treated patients.[82] This important study is summarized in Table 3.[82]

The role of *H pylori* eradication in gastric ulcer relapse has not been studied extensively. Graham and coworkers showed that the probability of gastric ulcers recurring after a year was 13% for patients treated with ranitidine plus triple-drug therapy compared with 74% in patients treated with ranitidine alone.[74] Seppalla and associates treated patients with *H pylori*-positive gastric ulcers with bismuth, bismuth plus metronidazole, or ranitidine. Of the 42 patients who remained *H pylori*-positive, 24 had a gastric ulcer recurrence compared with 0 of 10 recurrences in patients in whom *H pylori* was eradicated.[83]

TABLE 2.—*Recommended Triple-Drug Therapy Regimen to Eradicate* Helicobacter pylori *in the United States**

Medication	*Dose, mg/day*	*Duration, wk*
Bismuth subsalicylate tablets	262-525, 4×†	2
Tetracycline	500, 4×	2
Metronidazole	250, 3×	2

*From Logan et al and Graham et al.[64,65]
†One to two tablets.

TABLE 3.—*Pyloricidal Therapy for Active Duodenal Ulcer**

Clinical Features	*Patients Receiving Amoxicillin and Metronidazole† Plus Ranitidine HCl, No. (n=52)*	*Patients Receiving Placebo Plus Ranitidine HCl, No. (n=52)*
Diarrhea	7	1
Helicobacter pylori eradicated	46‡	1
Ulcer healed		
6 wk	48‡	39
10 wk	51	49
Remission at 52 wk	42	3

HCl = hydrochloride

*From Hentschel et al.[82]
†Dosage: amoxicillin, 750 mg 3 times a day, and metronidazole, 500 mg 3 times a day, each for 12 days.
‡$P < .05$ versus placebo.

Recommendations

Most cases of ulcer with *H pylori* infection are well managed with the effective and safe regimens currently available in the United States—H_2-receptor antagonists, sucralfate, antacids, or proton pump inhibitors. When antibiotic therapy for *H pylori* is indicated is not yet clear, nor is it clear which drugs achieve the best balance of safety, efficacy, and reasonable cost. It seems reasonable to treat patients in whom the benefits are likely to outweigh the risks, inconvenience, and extra cost of treatment. Ulcer patients with a diagnosis of *H pylori* (by histologic examination, serologic test, or breath test) and who have frequent symptomatic recurrences (≥ 2 per year) seem most suited for treatment. These are the same patients for whom maintenance therapy with a nocturnal H_2-receptor antagonist or elective surgical therapy—such as parietal cell vagotomy—are also reasonable considerations. It is no longer appropriate, however, to refer *H pylori*-infected patients with refractory ulcer disease for an

elective operation unless an attempt to eradicate *H pylori* has been made and has failed.

If treatment of *H pylori* is chosen, the best current regimen appears to be the following: bismuth subsalicylate tablets, 525 mg four times a day; metronidazole, 250 mg or 500 mg three times a day; and either tetracycline or amoxicillin, 500 mg four times a day, for two weeks. Such therapy will eradicate *H pylori* in 65% to 90% of patients.[84-90] If a more convenient, safe, and effective regimen to eradicate *H pylori* can be developed, pyloricidal therapy may prove to be more cost-effective than current maintenance therapy regimens involving H_2-receptor antagonists. Until that time, attempts at eradicating *H pylori* should be limited to outpatients with frequent or severe duodenal ulcer recurrences and to inpatients with duodenal ulcer complications such as bleeding, although studies in this latter group of patients have not yet proven efficacy. For this reason, it may be prudent to maintain H_2-receptor antagonist therapy in patients with bleeding duodenal ulcers to prevent rebleeding,[91] even if *H pylori* is eradicated. Finally, in those ulcer patients in whom an attempt is made to eradicate *H pylori*, it is not yet clear whether a subsequent endoscopy to document eradication is cost-effective. When a reliable, noninvasive urea breath test becomes widely available, the argument regarding the necessity for endoscopic documentation of *H pylori* eradication may become moot.

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Articles

Fatal Isoniazid-Induced Hepatitis
Its Risk During Chemoprophylaxis

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Isoniazid chemoprophylaxis has long been known to be a highly effective means of preventing silent tuberculous infections from spreading to active disease. There has been much controversy, however, about the risk it carries for fatal hepatotoxicity. In this article I review the rate of fatal isoniazid-induced hepatitis during chemoprophylaxis that is done according to current monitoring guidelines. Information was obtained from a MEDLINE literature search and a survey of tuberculosis control officers in large metropolitan areas throughout the country. Data were included of patients who were monitored according to the American Thoracic Society's guidelines or who were treated after 1983 when the guidelines were published. The pooled results of the published studies showed no hepatotoxic deaths in 20,212 patients in whom prophylaxis was started. The unpublished data showed 2 deaths in 182,285 patients, for a combined rate of 0.001% (2 of 202,497). The death rate for those older than 35 years was estimated to be 0.002% (1 of 43,334). This rate is significantly lower than was previously estimated and should be used to reevaluate the benefit of preventive therapy for tuberculin-reactive patients older than 35. The risk of fatal isoniazid-induced hepatitis is negligible for all ages when patients are routinely monitored for liver toxicity.

(Salpeter SR: Fatal isoniazid-induced hepatitis—Its risk during chemoprophylaxis. West J Med 1993; 159:560-564)

Isoniazid was introduced in 1952 and was considered a safe and effective treatment against tuberculous infections. From 1955 through 1967, approximately 100,000 patients on isoniazid chemoprophylaxis were observed, and only occasional cases of hepatotoxicity were noted.[1] After that time, however, several fatalities from isoniazid hepatitis were reported.[2,3] In 1972 a large survey of preventive therapy from the US Public Health Service (USPHS) showed 8 deaths in 13,838 persons (0.06%).[2] Most of the deaths were in persons with severe alcoholism, and all were in persons older than 35, indicating a death rate for this older age group of 0.1% (8 of 8,138). The patients had been evaluated monthly for symptoms, but no routine laboratory tests had been performed.

After the results of this study became known, the American Thoracic Society recommended that chemoprophylaxis be restricted to tuberculin-reactive persons who are at increased risk of tuberculosis developing or who are younger than 35.[4] It also advised that treatment be withheld in the presence of acute liver disease. The guidelines were revised in 1983 to include obtaining baseline and periodic liver function tests for those older than 35 years and discontinuing treatment if aminotransferase levels exceeded three to five times normal.[5] In this article I evaluate the rate of fatal isoniazid-induced hepatotoxicity that occurs when monitoring guidelines are followed.

Patients and Methods

Published Data

A MEDLINE literature search was done of English-language articles from January 1966 to August 1992 using the headings or text words "isoniazid" and "tuberculosis/prevention and control." Another search was done with the text words "isoniazid chemoprophylaxis" and "isoniazid preventive therapy." The search revealed 178 possibly relevant articles, and 78 additional citations were found from their references. Articles were chosen for evaluation if they described prospective clinical trials or epidemiologic surveys using isoniazid, with or without another antituberculous drug, to treat inactive or silent tuberculous infection. Patients with silent infection usually have a positive tuberculin skin test but are asymptomatic with normal chest radiographs. Inactive disease is generally manifested by stable chest radiographs before therapy and sputum smears negative for acid-fast bacilli. A few studies had patients with positive sputum cultures or with chest radiographs that improved with treatment. These patients were included in this study if their treatment regimen was the same as that for chemoprophylaxis.

The selection was further restricted to studies that monitored patients according to current guidelines. If an article did not describe the monitoring protocol com-

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ABBREVIATIONS USED IN TEXT

CDC = Centers for Disease Control and Prevention
HIV = human immunodeficiency virus
USPHS = US Public Health Service

pletely, it was included only if the study was done after 1983, when the guidelines were published.[5] Trials were excluded if they did not give data on the number of patients started on isoniazid therapy or the number of deaths from hepatotoxicity. Care was taken to record data on each group of patients only once, even if they were reported on in several articles. A total of 29 articles met the selection criteria and were evaluated further. There were 44 other studies on chemoprophylaxis, many well known, that were excluded because the authors did not monitor patients or did not supply information for calculating fatality rates, such as in retrospective studies, case-control trials, or case reports.

The studies were separated into two groups, those that used isoniazid alone and those that combined isoniazid with another antituberculous drug for the treatment of inactive disease. When available, information was obtained on the number of patients who dropped out due to hepatitis or other causes, were postpartum, were infected with the human immunodeficiency virus (HIV), or were older than 35. When incomplete age data were provided, the number of patients older than 35 was estimated from the available information. For example, when the number of people between ages 30 and 40 was known, half of them were estimated to be older than 35.

Unpublished Data

Surveys were sent to the tuberculosis control officers in 26 large metropolitan areas across the country, from a list supplied by the Centers for Disease Control and Prevention (CDC) (D. Brown, CDC, written communication, August 1992). All 26 control officers were contacted, and 19 were able to supply information on the rate of fatal hepatitis that occurred during isoniazid chemoprophylaxis in their areas since 1983, or since they began monitoring for liver toxicity.* The CDC provided information on four additional counties for 1990. Data were collected by reviewing the tuberculosis program management reports that had been compiled every six months and sent to the CDC. These reports contained information on the total number of persons starting and completing prophylaxis and the number who died of any cause during treatment. The tuberculosis control officers evaluated the cause of death from the medical records. Fatal hepatitis was defined as any death thought to be due to acute liver toxicity. When possible, data were obtained on age, completion of therapy, pregnancy status, and HIV infection.

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Results

Published Data

The information obtained from the 29 articles that fit the selection criteria is summarized in Table 1. A total of 16,705 patients were started on chemoprophylaxis with isoniazid alone, and no deaths from hepatotoxicity were reported.[6-31] Of the participants, 2,538 (15%) dropped out before therapy was completed, for a variety of reasons. Of all patients started on treatment, 1.8% stopped because of hepatitis. It was estimated from the available information that 7,900 (47%) of the participants were older than 35. One study contained information on 25 patients infected with HIV, and no monitored study on pregnant or postpartum women was found.

A total of 3,507 patients were started on therapy for inactive tuberculosis with a combination of isoniazid and another antituberculous drug, such as rifampin, streptomycin, or ethambutol, and no deaths from hepatotoxicity were seen.[30-34] In all, 126 patients (3%) dropped out before therapy was completed, and 21 (0.6%) showed signs of hepatitis. It was estimated that 800 patients (23%) were older than 35 years.

In summary, 20,212 patients were started on preventive isoniazid therapy, with no hepatotoxic deaths. Of these, 13% did not complete treatment, and hepatitis developed in 1%. An estimated 8,700 patients were older than 35.

Unpublished Data

Information on the rate of fatal isoniazid-induced hepatitis was obtained from 23 of the 26 counties that were surveyed; that information is summarized in Table 1. Two deaths from liver disease were reported among 182,285 patients started on chemoprophylaxis since 1983 (0.001%). According to the available information, 20% of the patients did not complete therapy for various reasons. Hepatitis developed in approximately 1.2% of those started on isoniazid, requiring discontinuation of treatment. In counties that supplied data on age, an average of 19% of the participants were older than 35 years. At least 6,050 postpartum women and 577 HIV-infected persons were included in the survey, with no deaths in these groups.

One of the two deaths reported was in 1983, in a 29-year-old man. It is unclear if he had other risk factors for hepatotoxicity, such as alcoholism. The other death occurred in an elderly man with colon cancer that was presumed to be metastatic to the liver. If the age distribution for all patients is extrapolated from the available data, the death rate for those older than 35 years is 0.003% (1 of 34,634). Seven of the tuberculosis control officers were unable to provide complete information on the number of people started on isoniazid since 1983 because detailed records had not been maintained, but none recalled any reports of fatal isoniazid hepatitis in their areas during that time.

Combined Results

Combining the data from the published studies and unpublished reports, there were 2 hepatotoxic deaths

TABLE 1.—*Summary of Published and Unpublished Data on Isoniazid Chemoprophylaxis for Tuberculosis*

		Deaths		Incomplete Therapy		Hepatitis		Age >35 yr	
Data Category	*No.*	*No.*	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*
Published data, isoniazid alone	16,705	0	--	2,538	15	251	1.8	7,900	47
Published data, combined therapy	3,507	0	--	126	3	21	0.6	800	23
Subtotal	20,212	0	--	2,664	13	272	1	8,700	43
Unpublished data, isoniazid alone	182,285	2	0.001	36,457*	20	2,187*	1.2	34,634*	19
Total	202,497	2	0.001	39,121	19	2,459	1.2	43,334	21

*Number extrapolated from available information.

among 202,497 persons started on isoniazid therapy, for a case-fatality rate of 0.001% (see Table 1). A statistical analysis of these data was done using the Poisson distribution with a one-tailed 95% confidence interval, which predicted that the true fatality rate could be no more than 0.003% (6 of 200,000). From the available age data, the death rate for those older than 35 years can be estimated as 0.002% (1 of 43,334). Using Poisson statistics, the upper limit for the true incidence of death in this age group would be 5 in 43,000, or 0.01% (1-tailed 95% confidence interval). No deaths were found in at least 6,000 postpartum women, 600 HIV-infected patients, and 3,500 persons on combined therapy. On average, 19% of patients did not complete treatment, and hepatitis developed in 1.2%.

Discussion

The results of this study indicate that when monitoring guidelines are followed, the risk of fatal hepatotoxicity from isoniazid chemoprophylaxis is negligible. In this study 2 deaths were reported among 202,497 persons started on isoniazid therapy, for a mortality of 0.001%. The age data provided in this study were incomplete, but if the age distribution for all patients is extrapolated from the available information, the death rate for those older than 35 was 0.002% (1 of 43,334). Although no deaths were reported in postpartum women, HIV-infected patients, or persons on combined therapy, the total number of patients was too low to assess the risk in these groups adequately. Further studies will be required to evaluate those risks. The rates used in this study assess the ratio of hepatotoxic deaths to the number of persons started on isoniazid therapy. This case-fatality ratio is an appropriate measure of the risk of placing a patient on the therapy. In this study, of the patients started on treatment, 81% completed therapy and acute hepatitis developed in 1.2%.

The rate of fatal hepatotoxicity found in this study is equivalent to the rate in the general population of death from acute hepatitis and acute liver necrosis from any cause (0.001%).[35] It should be noted that this rate does not include deaths from chronic liver disease and cirrhosis, which are much more common in the general population, occurring at a rate of 0.01%. For persons older than 35, the risk of death from any hepatic disease is approximately twice the average risk for all ages.[35] The present study found a similar age differential for fatal isoniazid-induced hepatitis.

The rate of fatal hepatotoxicity observed in this study is significantly lower than that from the USPHS trial, which was 0.06% with an age-adjusted rate of 0.1%.[2] Two possible explanations for this vast discrepancy are as follows:

- Many of the deaths in the USPHS survey could have been prevented if the current guidelines had been followed, such as excluding patients with acute liver disease and detecting early signs of toxicity with routine laboratory monitoring; and
- The USPHS trial had an unusually high death rate compared with other studies. It appears that 7 of the 8 deaths occurred in Baltimore in 1972, where the fatality rate for cirrhosis that year was substantially higher than in the rest of the country.[36]

When the data from other large trials that did not routinely monitor patients are combined, the rate of fatal hepatitis is 0.01% (8 of 60,000).[37-44] This rate, which is probably a more accurate estimate of the death rate in unmonitored patients, is still ten times higher than in the present study.

A recent report from the CDC reviewed 177 cases of fatal isoniazid-induced hepatitis from 1972 through 1988 that were found through a literature search and from personal communications.[45] Information was incomplete on the total number of persons started on isoniazid therapy throughout the United States during that time, so an accurate estimate of the case-fatality rate was difficult to make. If the information supplied by the tuberculosis control officers in state and local health departments is analyzed separately, however, the death rate is 0.005% (59 of 1,084,760). Most of the years covered by this report were before routine monitoring, so it is understandable that this rate is midway between those of the previously mentioned unmonitored studies (0.01%) and the present study (0.001%).

In this study the fatality rate may be underestimated if deaths due to hepatitis were not reported or were misclassified. This problem is inherent in all large surveys of this type. The tuberculosis control officers recently reviewed their records for the CDC study, and it is unlikely that they missed many cases recorded with adverse effects as serious as death. The fatality rate could also be underestimated if some deaths occurred as a result of chronic hepatitis after patients had completed their course of treatment. This is unlikely, however, because isoniazid-

related hepatitis has been studied extensively and is thought to occur as acute toxicity during therapy.[5]

It is also possible that the isoniazid-induced fatality rate has been overestimated in this study. One or both of the deaths reported may actually have been due to other causes of liver toxicity, such as liver metastases or alcoholic cirrhosis. The rate found would be even lower if all the control officers supplied the full number of persons started on isoniazid therapy since 1983, as they report no more deaths during that time.

There is no way to ensure that all of the patients included in this study were monitored exactly according to the guidelines. This situation is probably representative of what occurs in regular practice. It is reassuring to know that, even when the recommendations are not strictly enforced, the use of isoniazid is extremely safe.

If the rate of fatal isoniazid-induced hepatitis in monitored patients is truly equal to the rate of death from acute hepatotoxicity in the general population, then the recommendation to withhold chemoprophylaxis for those low-risk reactive persons older than 35 should be reconsidered. Decision analysis studies that used the USPHS rates concluded that for some subgroups of patients the risk of using isoniazid outweighed the potential benefit.[46-48] Other studies using an average fatality rate of 0.01% found that isoniazid was beneficial for reactive patients of all ages, even those at low risk of tuberculosis developing.[49-53] Lowering the risk of fatal hepatotoxicity even more by routinely monitoring patients would further increase the benefit-to-risk ratio for giving chemoprophylaxis to reactive persons of all ages.

If the data on isoniazid-induced hepatitis found in this study are used, a simplified decision analysis can be described to demonstrate the benefit of prophylaxis for different age groups. In persons who have been tuberculin reactive for many years without other risk factors, such as immunosuppression or abnormal chest radiographs, if not given prophylaxis, tuberculosis will develop at a rate of 0.2% per year, with an average associated mortality of about 10%.[54] Prophylaxis with isoniazid can decrease this risk by approximately 70%.[49] In other words, out of 100,000 low-risk tuberculin-reactive persons, 500 would die over the next 25 years without isoniazid prophylaxis, as opposed to 151 with prophylaxis. Only 1 of the 151 deaths would have been caused by isoniazid toxicity, with the rest due to tuberculosis. A person 70 years old may have a life expectancy of only 10 years, but the mortality associated with tuberculosis in this age group is increased to 17%.[51] In this case the mortality would be 340 deaths per 100,000 without preventive therapy compared with 104 with therapy. Of the 104 deaths, 2 would be due to isoniazid toxicity.

The incidence of tuberculosis is rising in the United States at an alarming rate, and in some places it is reaching epidemic proportions.[54] In a survey to evaluate the apparent failure to control tuberculosis, it was found that two thirds of the patients with active disease had never been screened and therefore had not been considered for prophylaxis.[55] Of those who had been given skin tests, more than half had a positive reaction, but two thirds of these reactive persons were never offered chemoprophylaxis. Another retrospective study was performed through the American Indian Health Service, where the current recommendation is to offer prophylaxis to all tuberculin-reactive persons regardless of age.[56] Approximately 75% of their tuberculosis cases might have been prevented if the standard American Thoracic Society guidelines for screening and prophylaxis had been followed. An additional 7% of patients had no known risk factors and would have been eligible for preventive treatment under the broader Indian Health Service guidelines. These results clearly indicate that greater attention to the recommendations for screening and prophylaxis could have a substantial effect on the control of tuberculosis.

Further studies are needed to verify the risk of fatal isoniazid-induced hepatitis in monitored prophylaxis. If the death rate is truly as low as this study indicates, we should consider expanding the recommendations to include prophylaxis for tuberculin-reactive persons of all ages who have no contraindications to treatment. If the guidelines for monitoring patients are followed carefully, widespread screening and preventive therapy could be used safely in an attempt to eradicate the disease. At the same time we must also look for other preventive treatment strategies, such as short-course multiple-drug regimens, that could increase patient compliance and combat the spread of drug-resistant tuberculosis.

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Articles

How House Officers Cope With Their Mistakes

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We examined how house officers coped with serious medical mistakes to gain insight into how medical educators should handle these situations. An anonymous questionnaire was mailed to 254 house officers in internal medicine asking them to describe their most important mistake and their response to it; 45% (N = 114) reported a mistake and completed the questionnaire. House officers experienced considerable emotional distress in response to their mistakes and used a variety of strategies to cope. In multivariate analysis, those who coped by accepting responsibility were more likely to make constructive changes in practice, but to experience more emotional distress. House officers who coped by escape-avoidance were more likely to report defensive changes in practice. For house officers who have made a mistake, we suggest that medical educators provide specific advice about preventing a recurrence of the mistake, provide emotional support, and help them understand that distress is an expected concomitant of learning from the experience.

(Wu AW, Folkman S, McPhee SJ, Lo B: How house officers cope with their mistakes. West J Med 1993; 159:565-569)

Many studies document that house officers experience considerable stress due to mistakes.[1-4] Little is known, however, about the strategies employed by physicians to cope with their mistakes and the extent to which these coping strategies affect their psychological well-being and subsequent medical practice. Information about the relationships among mistakes, coping, psychological well-being, and subsequent medical practice would help medical educators assist house officers to respond constructively when mistakes occur.

Research on other kinds of stress, including daily hassles, major life events, and chronic illness, suggest that some types of coping promote adaptive outcomes while other types of coping do not.[5-8] The judgment as to what constitutes adaptive or maladaptive coping in a given context depends on which outcomes are important in that specific context. Context must be taken into account because a particular coping strategy can be adaptive in one setting but maladaptive in another. For example, choosing not to think about a problem can be adaptive if nothing can be done, such as while waiting for test results, but can be maladaptive if problem solving and action are appropriate, as when a symptom appears that calls for medical attention.[9] In this study, we examined two outcomes that are important in understanding the consequences of residents' mistakes: the residents' changes in practice and psychological well-being. These outcomes reflect the two major functions of coping: a problem-focused function, in which coping is directed at the problem that is causing distress, and an emotion-focused function, in which coping is directed at managing the emotional distress caused by the problem.[9,10]

We previously reported how residents changed their practice following serious mistakes.[11] In this study we focused on the ways residents coped with their mistakes and how different ways of coping were related both to residents' subsequent changes in practice and to emotional distress. These analyses controlled for variables previously shown to be related to residents' reactions, including causes of the mistake, severity of the outcome, and institutional reactions.

Methods

In May 1989 we mailed an anonymous questionnaire to 254 house officers in three internal medicine training programs. Programs were located at large (greater than

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500 beds), academic, tertiary care hospitals. The procedures and development of the questionnaire have been described previously.[11]

Measures

Coping was measured using a shortened version of Folkman and Lazarus's "Ways of Coping" Scale.[12] The shortened version included six of the eight scales that make up the scale, and each comprised three items from the original scales. Scales measured the following kinds of coping: accepting responsibility, planful problem solving, seeking social support, emotional self-control, escape-avoidance, and distancing. Two scales, confrontive coping ("I tried to get the person to change his or her mind") and positive reappraisal ("I found new faith") were excluded because they did not seem relevant to medical mistakes. House officers were asked to indicate the extent to which they had used each strategy to cope after they made their mistake. An example of an item from the accepting responsibility scales is "I criticized or lectured myself" (Table 1). Possible responses were "not used," "used somewhat," "used quite a bit," and "used a great deal." Each type of coping was measured by summing responses to the three items in its scale. A higher score indicated a greater use of each strategy. The possible range of scores for each type of coping was 0 to 9.

TABLE 1.—*Ways of Coping Scale Scores and Item Frequency*

Ways of Coping (Cronboch's α)	*Scale Score** *Mean*	*SD*	*% Used†*
Accepting responsibility (.45)	4.9	2.0	
Made promise things would be different next time			76.3
Criticized or lectured self			62.3
Apologized or did something to make up			21.1
Planful problem solving (.62)	4.1	2.3	
Concentrated on what to do next			52.6
Knew what had to be done, doubled efforts to make up			40.4
Made a plan of action and followed it			38.6
Seeking social support (.69)	3.3	2.2	
Talked to someone about feelings			45.6
Accepted sympathy and understanding from someone			31.6
Asked a relative or friend for advice			22.8
Emotional self-control (.67)	3.2	2.1	
Tried to keep feelings from interfering with other things			51.8
Tried to keep feelings to self			22.8
Kept others from knowing how bad things were			13.2
Escape-avoidance (.60)	2.1	2.1	
Wished situation would go away or be over			30.7
Had fantasies how things might turn out			27.2
Tried to make self feel better by eating, drinking, using drugs or medications			1.8
Distancing (.60)	1.2	1.5	
Didn't let it get to me			9.6
Went on as if nothing had happened			6.1
Tried to forget the whole thing			5.3

*Range of possible scale scores, 0 to 9. Higher score indicates the coping strategy was used more.

†Includes those answering "used quite a bit" or "used a great deal."

The development of scales to describe residents' reactions to the mistake, institutional response, characteristics and causes of the mistake, and residents' subsequent changes in practice has been described previously.[11] Emotional distress in response to the mistake was measured with four items. Residents were asked to what extent the mistake made them feel remorseful, angry at themselves, inadequate, and guilty. A mistake was defined as having a serious outcome if the house officer reported that it resulted in a prolonged hospital stay, a specific procedure, a change in therapy, or death. Institutional response was measured with two items that asked residents how they felt the mistake was handled by the institution. Causes of the mistake were described by three scales: inexperience (3 items), job overload (2 items), and case complexity (4 items). Changes in practice were assessed with a scale of constructive changes in practice containing nine items and a scale of defensive changes containing two items. For each concept, scale scores were created by summing responses to items. Because constructive and defensive changes measure separate concepts rather than polar opposites of the same scale, a house officer might report both constructive and defensive changes in practice after making a mistake.

Analysis

We performed three multiple linear-regression analyses to investigate how residents' coping strategies were related to their emotional distress after the mistake, later constructive changes in practice, and later defensive changes in practice. These analyses controlled for variables previously found to be related to changes in practice: the perceived causes of the mistake, the severity of the outcome, the degree to which house officers perceived that their institution was judgmental, and house-staff gender.[11] The analyses tested whether the extent to which residents used each of the six ways of coping added significantly to the explanatory power of the independent variables.

Results

Characteristics of Respondents

As previously reported, of the 254 residents surveyed, 114 (45%) responded by reporting a mistake and completing the questionnaire. The 114 respondents who completed the questionnaire made up our study group. Because results did not differ by site, we present only aggregated results. Women comprised 33% of subjects. In all, 36% of respondents were interns, 32% were junior residents, and 32% were senior residents. The distributions of gender and year of training were similar among respondents and nonrespondents.

Coping

Residents indicated the extent to which they had used each of the six strategies to cope after they made their mistake. Table 1 shows responses for the Ways of Coping items and scales, as well as the percentage of respondents who reported they had used a strategy "quite a bit" or "a great deal." Mean scale scores were highest for accepting responsibility and planful problem solving, indicating that these strategies were most often used. Scores were somewhat lower for seeking social support and controlling emotions and still lower for escape-avoidance and distancing. For example, on the "accepting responsibility" scale, residents indicated they used the following strategies "quite a bit" or "a great deal": "I made a promise to myself that things would be different next time" (76%), "I criticized or lectured myself" (62%), and "I apologized or did something to make up" (21%). Examples of these strategies can be seen in the residents' narratives about their mistakes. For example, after failing to recognize the importance of and initiate therapy for ventricular tachycardia, a resident wrote, "I hung the EKG strip in my room with a sign saying "Next time, remember to . . ." One resident administered intravenous fluids to a patient with cardiogenic shock, mistakenly thinking the patient was septic, and induced congestive heart failure. The resident wrote, "I can occasionally rationalize that I was not the proximate cause of his death, as the patient was deteriorating slowly, but I must accept that I likely accelerated the course of his demise."

Distress

In multivariate analysis controlling for causes of the mistake, severity of the outcome, residents' perception that the institution was judgmental, and their gender, residents were more likely to report emotional distress if they coped by accepting responsibility. In addition, residents were somewhat more likely to report distress if they reported coping by seeking social support or by controlling their feelings. The multiple correlation coefficient (total R^2) for the model for emotional distress was .47 (Table 2).

As we reported previously, residents described considerable emotional distress in response to the mistakes, the large majority describing remorse, anger, guilt, and feelings of inadequacy.[9] For example, one resident mistakenly ordered benzodiazepine on an as-needed basis for a patient with respiratory muscle weakness. Subsequently, the patient suffered respiratory failure and died. The resident wrote, "Although his private MD and others assured me that the 'prn' Ativan was not the factor that tipped him over, I was never sure of that. To this day, I don't know if he would be alive had I made sure that no sedatives were [prescribed]."

Changes in Practice

As previously reported, house officers described making various changes in their subsequent practice as a result of the mistake.[11] Some of these changes were constructive, but others were defensive. For example, 72% of residents agreed somewhat or agreed strongly that as a direct consequence of having made the mistake, they were more likely personally to confirm data, 62% reported they were more likely to seek advice, and 52% that they changed the way they organized information. Other constructive changes included asking questions of peers or superiors, reading, asking for references, paying more attention to detail, changing the organization of data, and trusting others' judgment less. On the other hand, 13% reported discussing mistakes less, and 6% reported avoiding patients with similar problems.[11] In multivariate analysis, residents were more likely to report constructive changes if they coped by accepting responsibility, controlling for causes of the mistake, severity of the outcome, the degree to which house officers perceived that their institution was judgmental, and house-staff gender. None of the other coping strategies were independently related to constructive change. The total R^2 for the model for constructive change was .49. Residents were more likely to report defensive changes if they coped by escape-avoidance. None of the other coping strategies were independently related to defensive change. The total R^2 for the model for defensive change was .35 (Table 2).

TABLE 2.—*Relation of Ways of Coping to Emotional Distress and Changes in Practice**

	Emotional Distress		Constructive Changes in Practice		Defensive Changes in Practice	
Coping Strategy	β	P Value	β	P Value	β	P Value
Accepting responsibility	.67	.0001	.69	.02	.14	.02
Seeking social support	.27	.05	.36	.21	.11	.18
Emotional self-control	.28	.07	−.26	.46	.07	.28
Escape-avoidance	.21	.13	.25	.33	−.06	.34
Planful problem solving	−.11	.35	−.03	.90	.02	.72
Distancing	.07	.69	.02	.94	.01	.90
Total R^2	.47		.49		.35	
Adjusted R^2	.39		.41		.25	

*This model controlled for causes of the mistake, severity of the outcome, the degree to which house officers perceived that their institution was judgmental, and house-staff gender.

Discussion

In this study, house officers who coped by accepting responsibility were more likely than those who did not accept responsibility to make constructive changes in practice, but they were also more likely to experience emotional distress. These outcomes illustrate the complexity of coping. The same behavior was related to both positive and negative effects, and according to our definitions, such coping was both adaptive and nonadaptive.

Previous studies have examined how physicians cope with general daily stressors[13-20] and identified a variety of coping strategies. A few qualitative studies have investigated how physicians cope with mistakes and uncertainty.[17,19] These studies did not deal with responses to specific mistakes and did not examine the complexity of physicians' coping responses. No studies have examined how coping affects subsequent adjustment and practice, though a few studies suggest that coping strategies may play a role in modulating physician stress[13,18,20-22] or work satisfaction.[13]

In contrast, this study focused on specific mistakes, allowing each house officer to recall an actual situation and his or her response. Our study used a multidimensional approach to coping and assessed outcomes in terms of subsequent changes in practice and emotional distress. Our finding that the coping strategy related to a desirable outcome (change in practice) was also related to an undesirable outcome (emotional distress) has several important implications for medical education.

An important part of residency training is the acquisition of confidence and clinical competence. Dealing with specific problems and situations allows a resident to build a general sense of competence to deal with medical problems. Early in training, many residents suffer from insecurity about their own adequacy, and making a serious mistake can add to this insecurity. It is important that residents deal as effectively as possible with mistakes when they occur so that their general sense of competence is strengthened rather than weakened.

What can medical educators do to help a resident deal effectively with a serious medical mistake? We suggest that educators provide specific advice about preventing the recurrence of the mistake, provide emotional support, and help residents interpret their distress.

Cases in our study suggest how a review of the incident can promote constructive changes by both the resident and the institution. This review can lead to discussions of areas of uncertainty in clinical decision making, for example, when residents are faced with the decision of whether to act on an abnormal finding. Reviewing the case can suggest areas where residents should increase their knowledge. Such reviews may also point out signs that residents should be more aware of, such as agitation as a sign of hypoxia. Reviewing the case may also help attending physicians to suggest constructive changes in practice. For example, residents who misinterpreted arterial blood gases or electrocardiograms should be encouraged to study more in these areas. A resident who makes a mistake caused by a lapse in routine, such as failing to place a nasogastric tube in a patient with a history of hematemesis, may benefit from advice to resist the temptation to forgo established routines, particularly at the end of a shift or when tired. After a mistake, it also may be useful to discuss the potential for counterproductive changes in practice, such as avoiding procedures after experiencing a complication. In this case, further supervised instruction could prevent the development of a phobia about a procedure. Case review may also identify situations in which attending physicians might provide additional back-up. These include cases where residents felt overwhelmed by competing demands on their time or by too many patients. When these situations arise, it is important that residents be encouraged to call for help. Finally, a review of cases may lead to suggestions to improve features of the system of care that contributed to the mistake. Such features might include an excessive number of admissions for residents, inadequate mechanisms in the pharmacy to flag overdoses of drugs, or an inaccessibility of consultants.

Emotional support can be provided in several settings including house officer support groups and discussions of mistakes at departmental retreats. Levinson and Dunn have described a model of small group discussions of mistakes that has been well received by participants.[23] Crisis counseling can be a model for providing one-on-one emotional support by the attending physician.[24] The initial discussion should focus on the mistake and the residents' reactions. The attending physician should allow the resident to express his or her emotions, validate these reactions, and provide reassurance. Therapeutic referrals should be offered when needed. Next, the attending physician should assess how the resident is coping with the mistake. The house officer should be encouraged to accept responsibility for and discuss the mistake and should be discouraged from forgetting about or avoiding thinking about it. In doing so, the resident who takes responsibility for a mistake cannot be expected to feel good about it at the same time.

The attending physician can help the resident interpret his or her feelings of distress as part of the process of learning from a mistake. The attending can also lessen distress by correcting mistaken attributions, such as that a mistake signifies incompetence as a physician. Providing emotional support to residents who accept responsibility for mistakes may make it easier for the residents to accept responsibility for mistakes in the future. For example, one resident who inadvertently ordered an overdose of levothyroxine commented, "This mistake sticks in my mind partly because the patient's attending was so kind and understanding when I called to tell him of my error." Attending physicians can help residents understand that other physicians who have accepted responsibility and experienced emotional distress have improved their subsequent practice and can convey the expectation that residents and future patients will benefit from these experiences.

Our findings also suggest that attending physicians

need to make a conscious effort to get mistakes out into the open. The importance of these efforts is underscored by the finding that barely half of residents told their attending physician about their mistakes.[11] Our previous results suggest that morbidity and mortality rounds are not settings in which information about mistakes is likely to surface.[9] Instead, attending physicians should take the lead in making discussions of mistakes a routine part of training. In one training program orientation, interns are given a talk by a popular and respected faculty member who candidly describes mistakes that she has made and the general lessons they have taught her. Attending physicians can also incorporate a discussion of the inevitability of mistakes and the importance of discussing them into introductory remarks with a new team while attending on wards. Formal and informal sharing by faculty of their own personal experience with mistakes may help make such discussions more acceptable.

Limitations

Our findings may be limited in several important ways. First, because accounts of mistakes and changes in practice were anonymous, we have no external confirmation of the data. Second, the limited response rate, the relatively small sample size, and the surveying of only internal medicine residents at three large teaching hospitals limit the generalizability of our findings. Nonresponse may have occurred in a nonrandom fashion, both among house officers who coped by the complete denial of a mistake and among others who remained too troubled by a mistake to confront the questionnaire. Finally, some associations we found may be due to relationships between study variables and unmeasured confounding variables, rather than cause-and-effect relationships between variables. For example, unmeasured personality characteristics of house officers might cause them both to cope by accepting responsibility and to make constructive changes in practice. Further research is needed to determine whether efforts to improve residents' coping skills also promote constructive changes in practice.

Internal consistency reliability was only moderate for five of the six coping scales and was low for one scale (accepting responsibility). In general, coping scales have lower internal consistency than trait measures because of the nature of coping: if a person uses one strategy successfully, he or she is not likely to turn to others. Because the reliability of a scale is the ceiling of its possible correlation with other variables, low internal consistency would lead to underestimates of the effects of coping and does not weaken the significance of the associations we found. To achieve a greater precision of responses, researchers measuring physician coping in future studies should consider using the original full-length scales in the Ways of Coping questionnaire.[21] Also, although the factor structure of the accepting responsibility scale has been shown to be stable across different populations, future studies might reexamine the constructs and their items.

Conclusion

Physicians responsible for educating house officers need to help them cope with their mistakes. They should begin to think of how to help residents cope in ways that promote constructive changes, such as by accepting responsibility. They should also be prepared to provide emotional support and to help residents maintain their confidence and develop professionally as they deal with their mistakes.

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Conferences and Reviews

Hypersensitivity Pneumonitis

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Although the cause and development of most inflammatory and fibrotic interstitial lung diseases are unknown, both the antigenic stimuli and the immunopathogenic mechanisms that produce the syndrome of hypersensitivity pneumonitis have been well described. Hypersensitivity pneumonitis is a group of related inflammatory and fibrotic interstitial lung diseases that result from hypersensitivity immune reactions to the repeated inhalation of antigens derived from fungal, bacterial, animal protein, and reactive chemical sources. Immune complex-induced inflammatory reactions initiate acute lung injury; T cell-mediated hypersensitivity reactions perpetuate it and induce chronic inflammatory, granulomatous, and fibrotic responses in the interstitium of the lungs. Because the natural history of many interstitial lung diseases of unknown causes involves the progressive evolution through these same phases, knowledge about immune pathogenesis gained from studies of hypersensitivity pneumonitis may provide a way to understand the causes and development of other interstitial lung diseases.

(Kaltreider HB: Hypersensitivity pneumonitis. West J Med 1993; 159:570-578)

Most interstitial lung diseases, such as sarcoidosis and idiopathic pulmonary fibrosis, are inflammatory and fibrotic disease processes of unknown cause and of uncertain pathogenesis.[1] Interstitial and alveolar-filling lung diseases are characterized in their early stages by acute and chronic alveolar and interstitial inflammation and later by progressive interstitial fibrosis and distortion of the lung parenchyma. The syndrome of hypersensitivity pneumonitis is a group of inflammatory and granulomatous interstitial lung diseases for which the offending antigens are known and the immune and inflammatory mechanisms causing lung injury have been identified. Although hypersensitivity pneumonitis is not a frequently encountered clinical syndrome, it perhaps provides a paradigm for understanding the immunopathogenic mechanisms of lung injury, and this in turn may help us understand the pathogenesis of the broader category of interstitial lung diseases. In this article I review the clinical syndrome of hypersensitivity pneumonitis with emphasis on those features that relate to its development, and I describe the proposed mechanisms that produce interstitial injury, inflammation, and fibrosis. Readers are referred to several excellent reviews of hypersensitivity pneumonitis for additional clinical information.[2-6]*

*See also the editorial by M. Schuyler, MD, "Lessons From Hypersensitivity Pneumonitis," on pages 620-622.

Clinical Features of Hypersensitivity Pneumonitis

Etiology

Hypersensitivity pneumonitis (also called allergic alveolitis) is a group of related inflammatory interstitial lung diseases that result from hypersensitivity immune reactions to the repeated inhalation or ingestion of various antigens derived from fungal, bacterial, animal protein, or reactive chemical sources. A selected list of the various clinical syndromes of hypersensitivity pneumonitis and their causative agents is given in Table 1. Comprehensive lists are available elsewhere in general reviews.[2-4] The following are the most important groups of etiologic agents:

- The thermophilic actinomycetes that are responsible for farmer's lung, bagassosis, and humidifier lung[7-9];
- Avian serum proteins, which induce bird fancier's lung[10];
- Fungi such as *Aspergillus* and *Penicillium* species that cause malt-worker's and cheese-worker's lung and suberosis[11-13]; and
- Reactive chemical compounds such as toluene diisocyanate[14] and certain drugs.[15,16] The pathogenicity of an environmental agent depends on the chemical composition of the compound, the size of the inhaled particle, and the dose and duration of exposure.[5] The susceptibility or

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ABBREVIATIONS USED IN TEXT

BAL = bronchoalveolar lavage
Ig = immunoglobulin
IL-1 = interleukin 1
MHC = major histocompatibility complex
TNF-α = tumor necrosis factor-α

predisposition of the host to immune lung injury is also of critical importance because interstitial lung disease develops in only a few equally exposed persons.[17,18] Regardless of the etiologic agent or its environmental setting, the pathogenesis and clinical manifestations of these hypersensitivity lung diseases are identical, and the various syndromes can be considered as a single disease.

Pathogenesis

The pathogenesis of hypersensitivity pneumonitis requires ongoing or repeated exposure to the offending antigen.[19,20] During initial sensitizing exposures, the host generates appropriate immune responses to the antigen, which result in the generation of specific antibody and sensitized T lymphocytes. Later antigen exposure of sensitized persons produces lung injury in those who are predisposed to have hypersensitivity immune responses. The clinical syndrome of hypersensitivity pneumonitis results from the sequential and combined effects of two hypersensitivity reactions, as will be discussed in detail later.

Clinical Syndromes

Two distinct clinical syndromes with differing presentations and manifestations are recognizable[2-4]: acute and subacute or chronic hypersensitivity pneumonitis. The differing manifestations are determined by the intensity and frequency of antigen exposure. Episodes of the acute form result from intermittent intense exposure and are reversible. Symptoms of the acute disease occur four to six hours after exposure to the offending antigen and consist of the abrupt onset of a flulike syndrome characterized clinically by fever, chills, malaise, and myalgias. Pulmonary symptoms consist of severe dyspnea, chest tightness, and a nonproductive cough. Physical examination reveals fever, tachypnea, cyanosis, and bibasilar crackles in the lungs. The symptoms and signs clear when the exposure ends. In the absence of a history of illness occurring within hours of exposure to an identifiable agent, the clinical syndrome is indistinguishable from acute respiratory infection.

Subacute or chronic hypersensitivity pneumonitis results from continual low-level exposure to an antigen. The onset of the illness may be insidious, with few if any symptoms during the early stages of the disease process. Relatively late in the course of the disease, after interstitial inflammation and fibrosis have been established, the patient notes symptoms of increasing dyspnea on exertion, fatigue, anorexia, cough, and weight loss. The physical examination shows restricted ventilation, bibasilar crackles, and, in advanced cases, signs of respiratory and right-sided heart failure. These findings are nonspecific, appear to bear no temporal relation to exposure, and are characteristic of advanced, progressive interstitial lung disease of any cause. Only a detailed occupational, environmental, and drug ingestion history will suggest a possible origin for the lung disease.

Laboratory Features

Routine laboratory test results are nonspecific. During acute disease, there is a neutrophilic leukocytosis; the leukocyte count is normal during subacute and chronic episodes. Eosinophilia occurs in only 10% of patients, in contrast to other hypersensitivity lung diseases, such as asthma. Serum protein electrophoresis shows a polyclonal increase in immunoglobulin (Ig) levels, but the serum concentration of IgE is normal.

TABLE 1.—*Representative Syndromes of Hypersensitivity Pneumonitis*

Clinical Syndrames by Etiologic Category	*Major Causative Agents*	*Environmental Source*	*Reference*
Thermophilic actinomycetes			
Farmer's lung	*Foeni rectivirgula,* Thermoactinomyces vulgaris*	Moldy hay	Gruchow et al, 1981[7]
Bagassosis	*Thermooctinomyces socchari, T vulgaris*	Moldy pressed sugar cane	Salvaggio et al, 1969[8]
Humidifier lung	*T vulgaris, Thermoactinomyces condidus*	Contaminated humidifiers, air conditioners	Fink et al, 1976[9]
Avian proteins			
Bird fancier's lung	Avian proteins	Bird droppings, feathers	Boyd et al, 1982[10]
Fungi			
Malt worker's lung	*Aspergillus clavatus*	Moldy malt	Riddle et al, 1968[11]
Cheese worker's lung	*Penicillium caseii*	Cheese mold	Schlueter, 1973[12]
Suberosis	*Penicillium frequentans*	Moldy cork	Avila and Lacey, 1974[13]
Reactive chemicals†			
Hypersensitivity pneumonitis	Toluene diisocyanate, trimellitic anhydride	Plastics industry	Yoshizawa et al, 1989[14]
Drugs†			
Hypersensitivity pneumonitis	Amiodarone, gold, minocycline hydrochloride	Medications	Guillon et al, 1992[15]; Martin, 1991[16]

*Formerly *Micropolyspora faeni.*
†These form hapten-protein complexes.

Serologic Studies

Serum-precipitating IgG antibodies against the suspected antigen are usually demonstrable.[21] The presence of the precipitating antibody indicates intense exposure to antigen, but does not show a causal relationship between the antigen and the lung disease. T lymphocytes obtained from the blood of patients with hypersensitivity pneumonitis undergo proliferation and elaborate inflammatory cytokines in response to antigen stimulation in vitro.[2,22] Intradermal testing with purified preparations of antigen can induce a positive Arthus skin reaction.[4] These findings indicate sensitization of the B-cell and the T-cell limbs of the immune system and that the affected person is capable of mounting a hypersensitivity response to intradermal antigen. Precipitin analysis, antigen-induced lymphocyte proliferation, and skin testing are investigative tools that are not generally available for routine clinical use.

Radiographic Findings

During acute episodes of hypersensitivity pneumonitis, chest radiographs may be normal or may show various degrees of reticulonodular interstitial infiltrates at both lung bases.[2,3] Acute changes resolve spontaneously over a period of weeks in most cases. High-resolution computed tomographic scanning of the chest has proved to be a remarkably sensitive tool for detecting early interstitial changes in acute hypersensitivity pneumonitis.[23] Hilar adenopathy and pleural disease, particularly effusions, are rare. If the disease progresses to the subacute and chronic phases, chest radiographs show increasing evidence of diffuse interstitial fibrosis, honeycombing, and a progressive reduction in lung volumes.

Pulmonary Function

The pulmonary function abnormalities observed in hypersensitivity pneumonitis, as in other interstitial lung diseases, are characterized by a restrictive ventilatory defect. Specifically, there is a symmetrical reduction in lung volumes, particularly in vital capacity and total lung capacity, and a decrease in compliance accompanied by a reduction in the diffusing capacity for carbon monoxide. These physiologic abnormalities result from infiltration of the lung interstitium by inflammatory cells, fluid, and fibrous tissue. Evidence for airways obstruction is generally mild or absent except in chronic disease, when it may be present in association with bronchiolitis obliterans. Moderate hypoxemia and mild hypocarbia are present. In acute hypersensitivity pneumonitis, abnormalities in pulmonary function parallel the acute episodes; between episodes all may revert to normal. During chronic disease, particularly after the onset of interstitial fibrosis, the functional abnormalities are progressive and irreversible.[24]

Bronchoalveolar Lavage

Bronchoalveolar lavage (BAL) samples cells and molecules at or near the air-tissue interface of distal air spaces in the lung parenchyma.[3,19,25] Analysis of cells retrieved by BAL of established cases of subacute and chronic hypersensitivity pneumonitis reveals a pronounced increase in the percentages of lymphocytes, which may account for as much as 80% of the total cells recovered and reflect the lymphocytic inflammatory infiltrate of the interstitium and alveoli (lymphocytic alveolitis).[26] Most of the lymphocytes are T cells with a predominance of $CD8^+$ T cells (cytotoxic or suppressor cells).[27] Lymphocytes retrieved by BAL express T-cell activation markers and undergo antigen-specific proliferation when stimulated in vitro.[14,15,19] The lavage fluid contains increased concentrations of albumin, immunoglobulins,[25] complement components, and antibodies to the offending antigen.[14,21] Collectively, the results of BAL studies in established cases of subacute hypersensitivity pneumonitis demonstrate the presence of specific antibody and of specifically sensitized T lymphocytes in the microenvironment of the bronchoalveolar spaces. The usefulness of BAL is limited clinically, but can help establish the presence of a lymphocytic alveolitis.

Inhalation Provocation Studies

Inhalation provocation is an investigative procedure in which patients with suspected hypersensitivity pneumonitis are given an inhalation challenge with graded doses of highly purified preparations of the suspected antigen under controlled laboratory conditions.[28] The response to provocation is assessed clinically, physiologically, and biologically for evidence of acute hypersensitivity pneumonitis (Figure 1). A positive response consists of an accurate reproduction of the acute clinical syndrome. The response occurs four to six hours after inhalation antigen challenge of previously sensitized persons. An acute

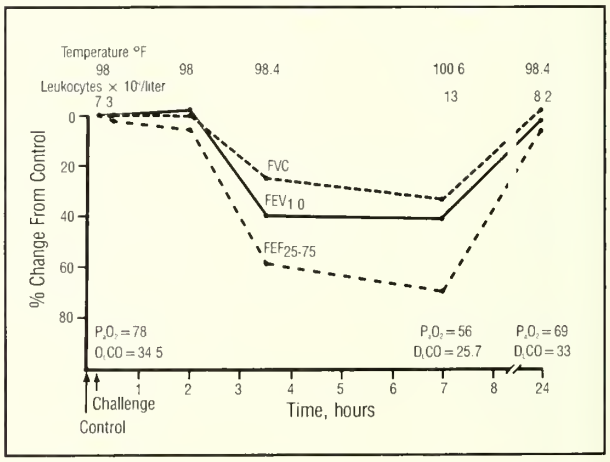

Figure 1.—The graph shows the typical response to inhalation provocation of a person with hypersensitivity pneumonitis. Fever and impairment of lung function begin about 4 hours after antigen challenge and resolve spontaneously 18 to 24 hours later. These responses are paralleled by leukocytosis, hypoxemia, and a reduction in diffusing capacity of the lungs for carbon monoxide (D_LCO). See text for details. (Reprinted with permission from Fink.[6]) FEF_{25-75} = forced expiratory flow between 25% and 75%, FEV_1 = forced expiratory volume in 1 second, FVC = forced vital capacity, PaO_2 = partial arterial pressure (tension) of oxygen

febrile illness develops with dyspnea, fever, and leukocytosis. There is a fall in the vital capacity, a reduction in the diffusing capacity, a rise in temperature, and hypoxemia. The abnormalities resolve spontaneously over a period of 18 to 24 hours. Although lung biopsies have not been done during inhalation provocation studies, BAL demonstrates abrupt increases in the levels of neutrophils, specific antibody, and complement components retrieved from alveolar spaces during the course of the reaction.[15,29] The results of provocation studies constitute the most compelling evidence for a causal relationship between a suspected antigen and acute hypersensitivity pneumonitis and provide strong biologic evidence for the role of immune complex-induced, neutrophil- and complement-mediated acute lung injury during the early phases of this disease. Although not generally available for clinical evaluation, and while posing some danger if not carefully performed, inhalation provocation can, when necessary, be used to establish definitively the causal role of an environmental antigen.

Pathologic Features

A clinical diagnosis of acute hypersensitivity pneumonitis can frequently be established on the basis of a thorough environmental and drug history, the characteristic history of the clinical syndrome occurring several hours after exposure, and the results of routine laboratory tests.[4] In their absence, such as frequently occurs with subacute and chronic disease, a lung biopsy may be necessary to suggest the diagnosis of hypersensitivity pneumonitis. Relatively little pathologic material has been obtained from patients in the early stages of acute hypersensitivity pneumonitis because the disease is self-limited. The material that is available shows interstitial deposition of immunoglobulin, complement, and antigen, the principal components of immune complexes, accompanied by mild obstructive bronchiolitis, but without vasculitis.[30] Most pathologic material has been obtained from patients with subacute and chronic hypersensitivity pneumonitis.[31] The characteristic findings consist of intense mononuclear inflammatory cell infiltrates in alveoli and interstitial spaces, consisting of lymphocytes, plasma cells, activated macrophages, and giant cells. As the disease progresses, the mononuclear cell infiltrates are accompanied by noncaseating granulomas, variable degrees of interstitial fibrosis, and remodeling of lung parenchyma. Mononuclear cell bronchiolitis and peribronchiolar fibrosis may also be present. These findings are characteristic of T cell-mediated delayed-type hypersensitivity reactions and of the granulomatous interstitial lung diseases, suggest the diagnosis of hypersensitivity pneumonitis, and should prompt a more detailed environmental history.

Diagnostic Approach

Acute hypersensitivity pneumonitis is fundamentally diagnosed clinically. A high index of suspicion based on a suggestive environmental history is the mainstay of diagnosis. The characteristic temporal relationship between exposure and the onset of the acute disease is strongly suggestive. Removing the patient from the suspected environment or discontinuing a suspected medication results in the spontaneous amelioration of symptoms. An exacerbation of symptoms after the patient reenters the suspected workplace or domestic environment provides strong circumstantial evidence for the cause and presumptively establishes the diagnosis. The offending antigen can be further identified from an analysis of serum-precipitating antibodies, but these tests are not generally available for routine clinical use. A positive test indicates intense exposure to the antigen and, in the proper clinical setting, suggests a causal relation between exposure and disease. Skin testing is of little value because the antigen preparations are inherently toxic. Bronchoscopy with BAL can help rule out infectious pathogens and document lymphocytic alveolitis with a $CD8^+$ T-cell prominence. This can help distinguish hypersensitivity pneumonitis from sarcoidosis, which is a $CD4^+$ T-cell alveolitis.

When the diagnosis is apparent clinically, lung biopsy is not needed. In cases in which an environmental agent is not suspected and the patient's condition worsens, histologic analysis can provide the first clue to the diagnosis. Open lung biopsy is required to obtain sufficient tissue; transbronchial lung biopsy specimens will not suffice. Inhalation provocation is investigational and should be reserved for selected patients in whom the causal relationship between antigen and lung disease must be established definitively.

Therapy

The mainstay of treatment is early diagnosis and the avoidance of exposure to antigen. The latter is accomplished by eliminating the offending antigen from the drug regimen or environment, wearing a respiratory protective device, or changing the nature of employment or the domestic environment. If successful, the syndrome of acute hypersensitivity pneumonitis will resolve spontaneously. A 7- to 14-day course of prednisone therapy, 0.5 mg per kg per day, will hasten the resolution of the acute disease. Subacute and chronic hypersensitivity pneumonitis, as with other inflammatory interstitial lung diseases, may require moderate to high doses—1.0 mg per kg per day—of prednisone for several months. The effectiveness of therapy should be monitored by clinical, radiographic, and physiologic measurements. Current practice dictates prompt and aggressive treatment of both the acute and subacute forms of hypersensitivity pneumonitis to prevent the progression of fibrosis.[24] The long-term beneficial effects of corticosteroids on arresting disease progression remain to be definitively established, however.[32]

Immune Pathogenesis of Hypersensitivity Pneumonitis

Initial Sensitization to Environmental Antigens

Normal immune responses to antigenic stimulation. Most environmental antigens that are relevant to the induction of interstitial lung diseases are complex, thymus-

dependent (T-dependent) antigens. Thymus dependency refers to the fact that helper T lymphocytes, or CD4+ T cells, are required to induce both B cell-mediated and T cell-mediated immune reactions. The normal physiologic response to stimulation by T-dependent antigens is the activation of both arms of the immune system (Figure 2).[33] To initiate immune responses, antigen-presenting cells such as macrophages engulf, process, and display immunogenic fragments of antigen on their surface membranes in association with class II molecules of the major histocompatibility complex (MHC). Specific binding of the class II MHC-antigen complex to the antigen receptor on CD4+ T lymphocytes results in the activation, proliferation, and differentiation of antigen-specific CD4+ T-cell clones into subsets of helper cells that help induce antibody production by B cells and that differentiate into T cells that affect cell-mediated immune functions. Under physiologic conditions, the major functions of fully differentiated T and B cells are to neutralize and eliminate antigen.

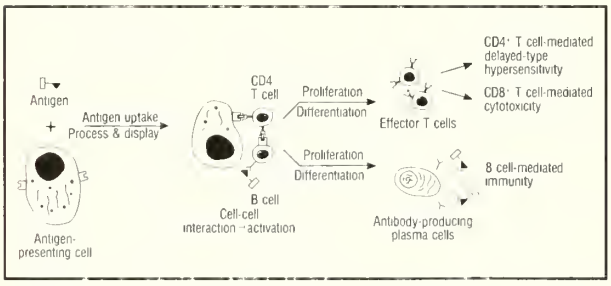

Figure 2.—The schematic shows the normal immune responses to a T cell-dependent antigen. Interactions among antigen-presenting cells, CD4+ T cells, and B cells result in the differentiation of both specific antibody-producing B cells and antigen-sensitized helper and effector T cells. T cells mediate cellular immune functions: effect delayed-type hypersensitivity and provide help for CD8+ T cell-mediated cytolysis. See text for details.

Normal immune responses in the respiratory tract. Antigenic stimulation of the respiratory tract induces specific immune reactions that are localized or compartmentalized in the airways and parenchyma of the lung. Inhaled antigens that penetrate normal pulmonary clearance mechanisms affect airway mucosa and bronchoalveolar spaces of the parenchyma. Foreign materials are engulfed by local phagocytes such as alveolar macrophages and are translocated by lymphatics to lymph nodes in the hilar regions of the lung where T and B cell-mediated immune responses are generated. These immune responses result both in the production of circulating antibody and in the clonal expansion of antigen-reactive B and T lymphocytes.[34,35] Activated lymphocytes recirculate and localize in the submucosa of airways and the interstitial and alveolar spaces of the lung parenchyma in response to antigen-induced inflammation.[36] In the pathogenesis of hypersensitivity pneumonitis, these immunophysiologic mechanisms induce the initial sensitization of persons to antigens.

Antigen-induced sensitization of the lung in hypersensitivity pneumonitis. The antigens that induce hypersensitivity pneumonitis are T cell-dependent, complex organic particulates or protein-hapten complexes.[19] In general these particulates are relatively resistant to intracellular digestion, contain adjuvant-like materials, and can directly activate macrophages and complement.[37] Consequently, these inhaled antigenic particulates induce nonspecific acute inflammation and stimulate specific immune responses in the respiratory tract. Asymptomatic persons with exposure to antigen do in fact generate B-cell and T-cell responses to inhaled antigens, as evidenced by the presence of precipitating IgG antibody and antigen-reactive T lymphocytes in blood[2] and by the increases in total number of T lymphocytes and specific antibody in BAL.[38] Persons with exposure to sensitizing doses of environmental antigens undergo immune stimulation, resulting in persistent lymphocytic alveolitis in the lung parenchyma.[19] Sensitized persons are susceptible to the development of symptomatic hypersensitivity lung disease following further exposure to the offending antigen.

Hypersensitivity immune responses to antigenic stimulation. Under physiologic conditions, immune responses provide protection against antigen-induced injury. Dysregulated and exaggerated immune responses result in hypersensitivity or allergic reactions that can produce acute and chronic tissue injury (Table 2). Hypersensitivity immune reactions include the following:

- IgE-mediated immediate hypersensitivity (type I),
- Cytotoxic autoantibody-mediated hypersensitivity (type II),
- Immune complex-mediated intermediate hypersensitivity (type III), and
- T lymphocyte-mediated delayed-type hypersensitivity and T cell-mediated cytolysis or suppression (type IV).

This classification of hypersensitivity mechanisms is oversimplified because many immunologically mediated diseases in humans involve more than one hypersensitivity reaction. Current evidence indicates that the pathogenesis of hypersensitivity pneumonitis involves sequentially two mechanisms: the immune complex-mediated hypersensitivity reaction, followed by the T cell-mediated delayed-type hypersensitivity reaction. The former mechanism initiates and mediates the syndrome of acute hypersensitivity pneumonitis and the latter mediates the subacute and chronic syndromes. It is unclear why clinical evidence of lung disease develops in only a minority of antigen-exposed persons, whereas in the majority of equally exposed persons it does not. Host susceptibility factors are clearly important, but neither atopy nor HLA haplotypes correlate with being susceptible to having hypersensitivity pneumonitis.[17]

Acute Hypersensitivity Pneumonitis

Pathogenesis of acute hypersensitivity pneumonitis. Immune complex-mediated hypersensitivity reactions appear to initiate acute lung injury in the early phases of hypersensitivity pneumonitis in humans (Figure 3).[39] The

TABLE 2.—*Hypersensitivity Immune Reactions*

Hypersensitivity Type	*Onset After Antigen Challenge*	*Immune Mediator*	*Mechanisms of Tissue Injury*
Type I			
Immediate	10 to 20 min	IgE antibody	Mast cell-derived mediators
Type II			
Cytotoxic autoantibody	Variable	IgG, IgM antibodies against self or altered tissue antigens	Complement-mediated lysis; recruitment and activation of leukocytes
Type III			
Immune complex-mediated, intermediate	4 to 6 hr	Precipitating IgG or IgM immune complexes	Complement activation: C3a, C5a; recruitment and activation of neutrophils and macrophages; generation of toxic mediators
Type IV			
T cell-mediated, delayed	24 to 48 hr	$CD4^+$ T cells	Cytokines: TNF-α, IFN-γ; activated macrophages; toxic mediators, fibrogenic factors
		$CD8^+$ T cells	Class I MHC-restricted T-cell cytolysis; suppression

IFN-γ = interferon gamma, MHC = major histocompatibility complex, TNF-α = tumor necrosis factor-α

precipitation of immune complexes in pulmonary interstitium is the initial event. Immune complexes form in situ in lung interstitium as a result of the interaction of the inhaled antigen and serum-derived IgG antibody present in lung tissue and alveolar spaces.[39] The local deposition of IgG immune complexes induces acute interstitial and alveolar injury characterized by an intense neutrophilic alveolitis and an increase in vascular permeability.[40,41] Immune complexes trigger two critical events: activation of the complement cascade, and activation of interstitial and alveolar macrophages. Complement activation generates C3a, which enhances vascular permeability, and C5a, which is a potent chemotactic and activation factor for neutrophils and macrophages.[29] Immune complexes also activate pulmonary macrophages to secrete potent proinflammatory cytokines, particularly interleukin (IL)-1 and tumor necrosis factor-α (TNF-α).[42] These cytokines induce the expression of adhesion molecules on leukocytes and on endothelial cells of the pulmonary microvasculature.[43] Adhesion molecules promote the obligatory adherence of neutrophils and subsequently monocytes to endothelium before they migrate into the alveolar interstitium in response to C5a.[44] Interestingly, the neutralization of TNF-α activity with specific antibody protects the lung against immune complex-induced alveolitis and prevents the influx of neutrophils.[45] Newly recruited neutrophils and macrophages are activated by the interaction of immune complexes with their Fc receptors. Activated neutrophils and macrophages elaborate and release proinflammatory and toxic mediators that include toxic oxygen radicals, hydrolytic enzymes, arachidonic acid metabolites, and inflammatory cytokines.[40] These mediators induce acute inflammatory injury and necrosis of the cellular and matrix components of the lung interstitium,[46] amplify the acute inflammatory response, and recruit the additional lymphocytes and monocytes that subsequently mediate delayed-type hypersensitivity reactions that induce subacute and chronic hypersensitivity pneumonitis.

Clinical evidence favoring immune complex-mediated injury in acute hypersensitivity pneumonitis in humans. There is compelling clinical evidence that immune complex-mediated hypersensitivity reactions contribute to the

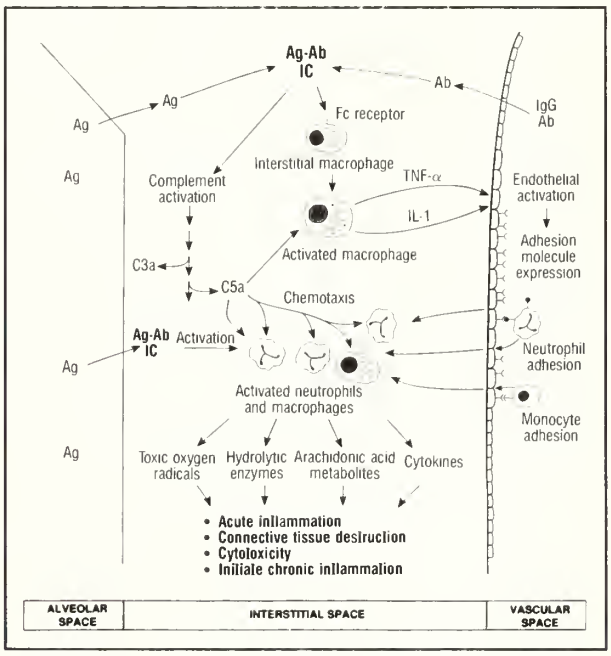

Figure 3.—The diagram represents immune complex-induced inflammation in the interstitium of the lung. The interaction of antigen **(Ag)** deposited in alveolar spaces with circulating IgG antibody **(Ab)** forms precipitating antigen-antibody immune complexes **(IC)** in interstitial spaces. Immune complexes trigger activation of both complement and pulmonary macrophages. Activated macrophages secrete cytokines (interleukin-1 [IL-1], tumor necrosis factor-α [TNF-α]) that promote adhesion of leukocytes to activated endothelium. Complement activation enhances vascular permeability (C3a) and attracts inflammatory cells (C5a). As a consequence of recruitment and activation, inflammatory cells release toxic mediators that induce acute lung injury. See text for details.

pathogenesis of acute hypersensitivity pneumonitis. First, the time course of the start of acute lung disease four to six hours after exposure to the offending antigen is identical to the established kinetics of immune complex-induced injury. Second, affected persons have high concentrations of precipitating IgG antibody in both serum and BAL specimens. This antibody is available to form immune complexes with antigens in the lung. Third, histopathologic material from patients with acute hypersensitivity pneumonitis demonstrates the presence in interstitial lung tissue of immunoglobulin, complement, and antigen, the principal components of immune complexes. Fourth, highly purified preparations of offending antigens induced a classical Arthus skin reaction in patients with hypersensitivity pneumonitis, demonstrating that the person is hypersensitive and can mount a cutaneous immune complex-mediated reaction. Finally, patients having acute pulmonary reactions induced by inhalation provocation show an increased number and proportion of neutrophils and increased concentrations of complement[29] and specific antibody in fluids retrieved by BAL of the lung. Collectively, these clinical observations strongly support immune complex-mediated lung injury in the initiation of acute hypersensitivity pneumonitis in humans.

Subacute and Chronic Hypersensitivity Pneumonitis

Pathogenesis of subacute and chronic hypersensitivity pneumonitis. T cell-mediated hypersensitivity reactions are clearly responsible for the lymphocytic, granulomatous, and fibrotic interstitial inflammation characteristic of the subacute and chronic phases of hypersensitivity pneumonitis (Figure 4).[4,19,47] T lymphocyte-mediated, delayed-type hypersensitivity reactions supervene within 24 to 48 hours after the onset of immune complex-induced acute lung injury. Immune complexes and C5a activate interstitial macrophages, inducing them to elaborate proinflammatory cytokines, particularly IL-1 and TNF-α.[48] These cytokines potently induce the expression of adhesion molecules on leukocytes and on vascular endothelial cells.[49] Adhesion molecules facilitate the adherence and subsequent transvascular migration of lymphocytes and monocytes into inflamed lung tissue[50] in response to chemotactic factors including antigen itself, IL-1, IL-2, lymphocyte chemotactic factor, and C5a.[36] Circulating, antigen-reactive, memory CD4+ T lymphocytes, generated by previous sensitization, migrate into lung parenchyma in response to chemotactic stimuli generated at foci of acute inflammation.[36] Within the lung interstitium, the interaction of antigen with antigen-presenting cells and CD4+ memory T cells initiate activation, clonal proliferation, and the differentiation of CD4+ T cells into multiple subsets, producing cytokines that generate the delayed-type hypersensitivity reaction.[33] A central feature of delayed-type hypersensitivity reactions is the potent activation of macrophages by interferon gamma derived from activated CD4+ T cells.[51] Activated pulmonary macrophages elaborate and secrete proteolytic enzymes and toxic oxygen radicals that induce lung injury.[52] The CD4+ T cell-derived proinflammatory cytokines recruit and activate additional monocytes and lymphocytes and prolong the inflammatory response. Ongoing antigen stimulation produces chronic delayed-type hypersensitivity reactions. These reactions induce immune granuloma formation[47] and activate macrophages to elaborate polypeptide growth factors that stimulate fibroblast proliferation and collagen synthesis resulting in interstitial fibrosis.[53,54]

Role of CD8+ T cells. T lymphocyte-mediated reactions include both CD4+ T cell-induced delayed hypersensitivity and CD8+ T cell-mediated cytotoxicity (Figure 2). It is striking that CD8+ T cells are present in large numbers in lungs of patients with hypersensitivity pneumonitis,[27,55] but their role in inducing or modulating hypersensitivity lung injury is not known. Functionally, CD8+ T cells comprise two major subgroups: cytotoxic T cells that effect antigen-specific, class I MHC-restricted cytotoxicity of cells infected with viruses and certain intracellular pathogens; and suppressor T cells that spe-

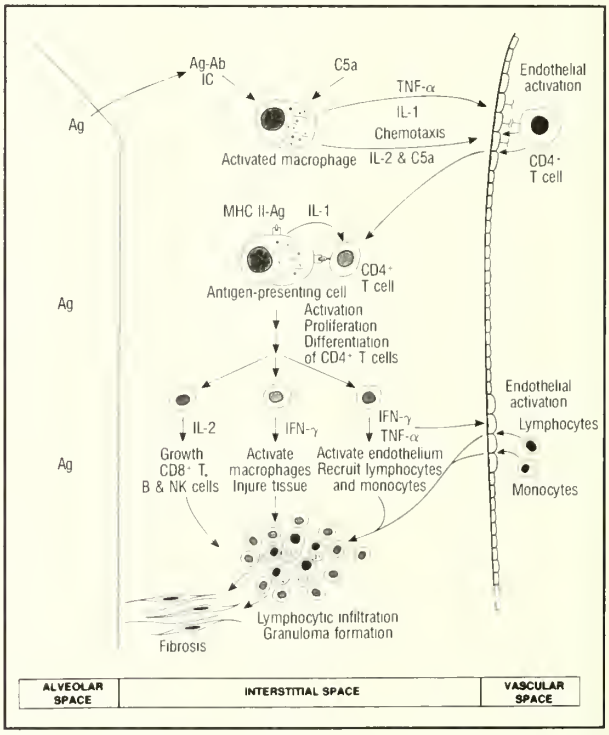

Figure 4.—The diagram represents a T cell-mediated delayed-type hypersensitivity reaction in the pulmonary interstitium. Pulmonary macrophages activated by immune complexes and C5a secrete several inflammatory cytokines that activate endothelium and recruit antigen-reactive CD4+ T cells into the interstitium from the vascular space. The interaction of antigen-presenting cells with the recruited CD4+ T cells results in proliferation and differentiation into a family of lymphokine-secreting T cells that affect several functions critical to the delayed hypersensitivity response: the growth of lymphocytes, activation of macrophages, and additional recruitment of mononuclear inflammatory cells. Chronic antigen stimulation results in lymphocytic and granulomatous interstitial pneumonitis and subsequently in fibrosis. See text for details. Ab = antibody, Ag = antigen, IFN-γ = interferon gamma, IL-1 = interleukin-1, MHC = major histocompatibility complex, NK = natural killer, TNF-α = tumor necrosis factor-α

cifically inhibit immune responses to antigen. Although lymphocytes retrieved by BAL from patients with hypersensitivity pneumonitis exhibit both cytotoxic and suppressive activity in vitro,[55] the cytotoxicity appears to be mediated by natural killer cells rather than by cytotoxic $CD8^+$ T cells.[56] The importance of both $CD8^+$-mediated cytotoxic reactions and the $CD8^+$ T-cell suppressive activity in the regulation of hypersensitivity lung disease is unclear.[55,57,58] Activated $CD8^+$ T cells can secrete inflammatory cytokines that promote adhesion and chemotaxis of additional T lymphocytes.[36,59] The major function of $CD8^+$ T cells may be to amplify and perpetuate $CD4^+$ T lymphocyte-mediated hypersensitivity reactions through the elaboration of cytokines in the lung.

Clinical evidence supporting T lymphocyte-mediated injury in subacute and chronic hypersensitivity pneumonitis. There is strong clinical evidence that T cell-mediated delayed-type hypersensitivity reactions induce lung injury in subacute and chronic hypersensitivity pneumonitis in humans. First, antigen-reactive memory T lymphocytes are present in both blood and lungs of affected patients. These T cells undergo proliferative responses to antigen stimulation in vitro, and expanded clones of antigen-reactive T lymphocytes are available for recruitment into the lungs in vivo. Second, histologic examination of lung biopsy specimens obtained from patients with subacute and chronic disease characteristically reveals intense lymphocytic and mononuclear interstitial infiltrates, immune granulomas, and interstitial fibrosis. These features are the hallmarks of T cell-mediated delayed-type hypersensitivity reactions. Third, animal models of hypersensitivity pneumonitis have consistently shown that T lymphocytes, particularly antigen-reactive $CD4^+$ T lymphocytes, are necessary for induction and for the adoptive transfer of hypersensitivity lung disease.[60] Clinical observations in human lung disease and in experimental models indicate that the subacute and chronic forms of hypersensitivity pneumonitis result from T lymphocyte-mediated hypersensitivity reactions.

Conclusions

Hypersensitivity pneumonitis is unique among the interstitial lung diseases because the offending antigens and the hypersensitivity immune mechanisms producing the inflammatory lung injury are known. It appears likely that immune complex-mediated hypersensitivity initiates acute lung injury and induces the syndrome. It is clear that T cell-mediated hypersensitivity mechanisms perpetuate acute injury and induce the inflammation, granuloma formation, and interstitial fibrosis characteristic of subacute and chronic hypersensitivity pneumonitis. It is significant that the strongest evidence to support the pathogenic roles of immune complex-mediated and T cell-mediated hypersensitivity reactions in hypersensitivity pneumonitis is derived from basic and clinical studies of the human disease.

Do the mechanisms identified for the pathogenesis of hypersensitivity pneumonitis constitute a paradigm for understanding the pathogenesis of other inflammatory interstitial lung diseases of unknown cause? A general feature of many interstitial lung diseases, including idiopathic pulmonary fibrosis, is that they begin with an acute cellular phase, progressively evolve through a chronic inflammatory phase, and terminate in a fibrotic phase that distorts the lung parenchyma and interferes with gas exchange. Unlike for hypersensitivity pneumonitis, however, the toxic agents that initiate acute lung injury and the pathogenic mechanisms that perpetuate injury are unidentified for most interstitial lung diseases. Toxic agents reach and injure the interstitium by either the pulmonary vascular or the inhalational route. The lung injury invariably provokes an acute and chronic inflammatory response within the interstitium, and this may result, in part, from specific hypersensitivity immune reactions to the toxic agent. Immune complex-mediated mechanisms may initiate acute inflammation and lung injury in the evolution of several idiopathic interstitial pneumonias.[39] Certainly during the cellular phases of interstitial lung diseases, such as sarcoidosis and lymphocytic interstitial pneumonitis, in which lymphocytic and granulomatous infiltration is so prominent, T cell-mediated mechanisms of lung injury are highly suspect.[33,47]

Some offending agents are clearly directly toxic to lung interstitium without the participation of immune reactions. Others, such as the agents that induce hypersensitivity pneumonitis and mycobacterial and fungal infections, induce injury predominantly, if not exclusively, through immunologically induced inflammatory responses. Thus, it is likely that the pathogenic mechanisms that induce inflammatory and infiltrative interstitial lung diseases represent a spectrum that ranges from nonspecific toxicity to hypersensitivity immune injury, with each disease resulting from a unique combination of pathogenic mechanisms. Hypersensitivity pneumonitis presents a unique model of lung injury in humans that serves as a paradigm for the development of hypothesis-testing experimental and clinical investigations of other forms of inflammatory interstitial lung diseases.

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Androgen Deficiency and Aging in Men

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Androgen levels decrease with age in men. Androgen deficiency in men older than 65 years leads to asthenia, a decrease in muscle mass, osteoporosis, and a decrease in sexual activity. Androgen deficiency has been reported to cause changes in mood and cognitive function. The combination of these factors results in impaired quality of life in older men. Androgen replacement therapy in hypogonadal men increases bone and muscle mass, enhances muscle and cardiovascular function, and improves sexual function and general well-being; whether elderly men experience benefits of androgen replacement is not known. These benefits have to be weighed against the possible adverse effects of prostate and cardiovascular diseases. Careful long-term studies are needed to assess the risk-to-reward ratios of androgen or other hormone replacement therapy before treatment strategies similar to estrogen therapy for postmenopausal women are implemented.

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In women, acute clinical symptoms of estrogen deficiency frequently accompany the onset of menopause. Sex hormone replacement therapy is generally recommended for postmenopausal women to diminish symptoms such as hot flashes and to reduce long-term manifestations such as osteopenia and bone fracture.

In men, the decline in androgen secretion occurs more gradually than the decline in estrogen secretion in women, and it has fewer acute clinical manifestations. Long-term androgen deficiency, however, leads to impaired sexual function, a decrease in muscle mass, and osteoporosis. The last two problems may predispose to frailty and an increased fracture rate. The beneficial effects of androgen substitution in men older than 65 years* have not been adequately documented, nor have the potential adverse effects of androgens on the prostate, plasma lipids, and red cell mass been studied in older men. Androgens may have direct actions in some tissues. In others, they may interact with other growth factors to manifest their full biologic activities. In this review, we describe the changes in spermatogenesis, sexual function, cognitive ability, bone mass, muscle strength and mass, cardiovascular function, and levels of androgens (such as testosterone) and nonandrogenic anabolic hormones such as growth hormone and insulinlike growth factor-I (IGF-I) with aging in men. We also consider the risk-to-reward ratio of possible benefits and adverse effects of androgen therapy in elderly men.

*Men differ from women in the time of onset and the development of senescent changes in the reproductive hormonal system. Menopause (in women) occurs over a few months to years, but the decline in men is slow and progressive, beginning sometime after age 30 and declining slowly thereafter. For many years the decrease in serum testosterone levels is not clinically discernible, but during the seventh decade symptoms and metabolic effects are common.

Androgen Levels in Elderly Men

A decline in serum levels of testosterone with aging has been reported in multiple cross-sectional studies of elderly men, with a considerable proportion falling below the normal range for young men.[1-7]* The metabolic clearance and production rates of testosterone have been shown also to be lower in elderly men.[1,4] The circadian rhythm in serum testosterone levels—higher in the morning, lower in the evening—observed in younger men is also lost in older men.[8] This may explain the inability to show an age-related decline in testosterone levels in some studies using specimens obtained in the afternoon. When integrated 24-hour or morning testosterone levels are measured, the concentrations are lower in the elderly. Limited longitudinal data on a small number of subjects confirm the decline of hormonal secretion with aging reported in cross-sectional studies.[5] This decline in total serum testosterone levels may be influenced by the health and physical fitness of the subjects. In studies where exceptionally healthy old men are studied, hormonal levels may be in the normal range despite advancing age.[9-11] Even though serum total testosterone levels may be normal in some elderly men, the levels of free (non-protein bound) or bioavailable (non-sex hormone-binding globulin bound) testosterone are often decreased. This is because levels of sex hormone-binding globulin increase with age, leading to lower levels of free or bioavailable testosterone.[2-4,6,12-15] Longitudinal data are limited on the relative change of serum-free or bioavailable testosterone levels in individual persons as they age. Some investiga-

*See also the editorial by A. M. Matsumoto, MD, "'Andropause'—Are Reduced Androgen Levels in Aging Men Physiologically Important?" on pages 618-620.

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ABBREVIATIONS USED IN TEXT

FSH = follicle-stimulating hormone
HDL = high-density lipoprotein
IGF-I = insulinlike growth factor-I
LDL = low-density lipoprotein
LH = luteinizing hormone

tors think that most men have a progressive decrease in serum testosterone concentrations as they get older. In contrast to testosterone, serum 5α-dihydrotestosterone levels are either slightly reduced or unchanged with aging, perhaps reflecting an increased production of dihydrotestosterone by the prostate in elderly men.[6,11,12] Levels of other androgens and metabolites such as androstanediol, androstanediol glucuronide, and dehydroepiandrosterone have been reported to decline between ages 40 and 70.[6] In most studies, levels of estrogens are not changed in elderly men.[4,6,9,13,16]

The mechanisms causing lower testosterone levels in healthy elderly men include a decreased responsiveness of Leydig cells to luteinizing hormone (LH) and a blunted compensatory elevation of LH to the lower testosterone levels. The primary testicular defect in the elderly is evidenced by a low Leydig cell mass,[17] a low testosterone production rate,[1] and a diminished testosterone response to exogenously administered LH or human chorionic gonadotropin.[3,9,18] Although most studies show elevated mean levels of LH and follicle-stimulating hormone (FSH) in aged men,[3,4,13,19] the increase in gonadotropins may be inappropriately low compared with the levels found in younger men with similarly decreased testosterone levels.[15,16] The occurrence of a secondary hypothalamic-pituitary defect in elderly men is further supported by the reports of decreases in the relative responsiveness of LH and FSH to gonadotropin-releasing hormone.[3,11,19,20] Low bioactive versus immunoreactive levels of LH and FSH[21,22] and alterations in LH pulse frequency and amplitude have been reported in elderly men.[23,24] The consensus from these studies is that serum testosterone and in particular bioavailable testosterone levels decrease with aging in men and that hypogonadism in elderly men is consequently a combination of testicular and hypothalamic-pituitary dysfunction.

Reproductive Function

An abrupt cessation of reproductive capacity, comparable to the menopause, does not occur with aging in men. Studies on spermatogenesis from autopsy specimens in elderly men showed substantial decreases in daily sperm production rates, testicular parenchyma tissue, seminiferous tubule volume, Sertoli cell numbers, and round spermatids compared with younger men.[17] Studies examining semen measurements from elderly men generally confirm the histomorphometric findings. Nieschlag and co-workers reported that healthy older men had higher sperm concentrations and lower sperm motility than younger men.[11] The ejaculate volume, sperm structure, and sperm fertilizing capacity as assessed by the zona-free hamster oocyte test did not decrease with aging. The duration of abstinence was longer in the older men and could have accounted for the increased sperm concentration and decreased motility. In another study Tsitouras showed that when the duration of abstinence was controlled at between two and three days, lower ejaculate volume, greater sperm motility, and percentage of spermatozoa with normal structure were reported in elderly men.[25] The actual fecundity of elderly men is not known, although a gradual decrease in fertility with aging has been reported.[26] The relationship between reduced androgen production and altered spermatogenesis in elderly men remains unclear.

Androgens, Psychosexual Function, and Cognitive Ability

Similiar to serum androgen levels, sexual activity and libido decrease with age in elderly men.[18,25,27] In most men with age-related sexual decline, however, factors other than decreased hormonal secretion (impaired penile vasculature, depression, chronic illness, pharmacotherapy) may also play a role. Well-controlled research has shown that testosterone therapy enhanced sexual desire and sexual fantasy in nonelderly hypogonadal men.[28] In elderly men, decreased libido and impotence present a common and important clinical problem. Although androgen replacement has been shown to enhance sexual function in many elderly men with low testosterone levels,[29,30] it cannot be assumed that androgen deficiency is responsible for impaired potency in older men when testosterone levels are in the normal range. Furthermore, no data are available to judge the effect of falling testosterone levels as men age when testosterone concentrations are still within the normal range. The threshold for testosterone effects on the libido in young men and young adult animals appears to be lower than that for many other metabolic functions,[31] but well-designed similar studies in older men are limited.

Evidence for hormonal effects on cognitive functions comes from studies showing relationships between testosterone and visuospatial ability in young men[32] and from a study showing changes in cognitive abilities with seasonal changes in testosterone levels.[33] In addition, a recent study found that hormonal treatment enhanced performance on the block design subtest of the Wechsler Adult Intelligence Scale in elderly men, whereas placebo treatment did not.[34] Similarly, in women with surgically induced menopause, memory and sexual functioning have improved following estrogen-androgen administration.[35] Thus, it is possible that age-dependent decreases in visuospatial ability, memory, and sexual functioning relate in part to a decline in testosterone levels.

Androgens and Osteoporosis

Although far greater attention has been given to the incidence of osteoporosis and fractures in aging women, an increasing incidence of osteoporotic fractures in aging men has been documented[36,37] and poses a major health problem. Bone density measurements show a progressive

decline with age in elderly men.[38-41] The risks of fractures in both men and women about double every five years after the age of 50.[37] A recent study of 30,000 men older than 40 years and 27,000 women older than 55 years in Finland showed that with aging, men had a greater risk of sustaining a thoracic vertebral fracture than women.[42] Because of the relatively few studies of aging in men, the pathogenesis of male osteoporosis is unclear; it has been suggested that declining gonadal function may be a major factor. Androgen receptors have now been demonstrated in human osteoblasts,[43] and androgens have been shown to induce the replication of human osteoblasts in vitro[44] and to modulate osteoblast function.[45]

Hypogonadism in men is associated with an increased risk of fractures.[46] Premature osteoporosis occurs in hypogonadal men in association with hypothalamic dysfunction, hyperprolactinemia, anorexia nervosa, Klinefelter's syndrome, and castration.[47-51] Androgen replacement therapy in osteoporotic men with clinically apparent hypogonadism[52,53] or correction of the low serum testosterone levels of hyperprolactinemia[48] is associated with an improvement in bone density. The few studies reporting bone histomorphometry do not agree on whether the osteoporosis of androgen deficiency is a low-turnover or high-turnover state.[48,49,52] In some patients urinary hydroxyproline excretion, a marker of bone resorption, has been found to be elevated.[47,51] In only one study have the newer tests of osteoblast function, including serum osteocalcin and bone-specific alkaline phosphatase activity, been assessed, and they were found to be elevated.[51]

Although decreased androgen secretion (low serum androgen levels) and osteoporosis are commonly seen in aged men, the causal relationship of the altered androgen levels and osteopenia are less clear. In men with vertebral crush fractures, 16% were found to have hypogonadism.[54] Early studies by Foresta and associates showed a positive linear correlation between the percentage of cortical area of the left second phalanx and serum testosterone or androstenedione levels in 30 elderly men.[55] Another study showed that vertebral bone density assessed by computed tomography in 60 healthy men (ages 30 to 92 years) correlated strongly with the free testosterone levels.[56] In another cross-sectional study of 48 healthy men (ages 21 to 79 years), bone mineral density at the spine and femoral neck (measured by dual-photon absorptiometry) was not correlated with sex hormone levels, but the bone mineral density at the radius was predicted by free testosterone levels and by body weight.[57] In one study in a nursing home population of white men older than 65 (mean age 77), 27% of the men had free testosterone concentrations below the normal range for the general population. In those with minimal-trauma hip fractures, 59% had hypogonadism as compared with 18% of the controls.[58] A recent study of 13 elderly men showed that testosterone replacement led to decreases in urinary hydroxyproline levels, suggesting a decrease in bone turnover. A preliminary report in 5 hypogonadal elderly men showed an increase in bone mineral density after testosterone replacement therapy.[60]

Androgens, Physical Exercise, Muscle Strength, and Function

Testosterone replacement in elderly men may have other benefits. Cross-sectional and longitudinal studies in elderly men show that lean body mass decreases and body fat increases with aging.[61-63] Although androgens are widely used by athletes and body builders, the evidence that their use increases muscle mass and muscle strength in normal men remains inconclusive.[64,65] A recent study in a small number of healthy men suggests that testosterone may increase muscle mass by increasing muscle protein synthesis.[66] The treatment of young healthy men and men with muscular dystrophy with testosterone administration for three months increased the basal metabolic rate and lean body mass.[67] In hypogonadal men, the replacement of androgens led to nitrogen retention, an increase in muscle mass, and a loss of adipose tissue.[64] Although it is not certain whether androgen replacement therapy will increase lean body mass, improve muscle strength, and decrease body fat in elderly men, some data are supportive. Tenover reported that short-term replacement therapy increases lean body mass and muscle mass in elderly men.[59] Muscle mass has been shown to be predictive of muscle strength in the elderly.[68] Muscle strength and physical activity are predictors of bone mass in women.[69,70] In elderly men, body composition, aerobic capacity, and muscle strength correlate strongly with bone mineral density.[71] Thus, improved muscle strength with androgens, physical activity, or both may also contribute to increases in the bone mineral density.[72]

Endogenous androgen levels are substantially influenced by physical exercise. As with growth hormone, the increase in circulating testosterone levels occurs within a short period of time (minutes) of the start of exercise.[73-75] Factors like nutritional status and the degree of exercise training are known to influence the testosterone response. Researchers have suggested that the increase in testosterone after exercise may be due to dehydration or to reduced hepatic flow with resultant decreased metabolic clearance. Exercise-induced secretion of testosterone is less in the elderly, similar to the growth hormone response to exercise.[76] There is some evidence that exercise-induced testosterone plays a role in the training effect—the phenomenon of muscle growth and hypertrophy that accompanies physical training. Thus, a cycle of physical inactivity, reduced endogenous testosterone secretion (or other growth factors), and decreased muscular function could likely contribute to the physical frailty that worsens the quality of life of many elderly people. Whether exercise alone or exercise in combination with exogenous testosterone administration can mitigate the well-described age-related reduction in exercise capacity is not known. Moreover, although training programs in older persons clearly improve cardiorespiratory fitness,[77] the mechanism of these changes remains unknown.

Growth Hormone and Insulinlike Growth Factors

In addition to low androgen levels, aging is associated

with low growth hormone and IGF-I secretion in men. Although baseline growth hormone levels appear to be unchanged, the total growth hormone peak area and the amplitude of the peaks are usually decreased in men older than 65 years.[78-80] In addition to the decreases in the pulsatile secretion of growth hormone, studies have shown low serum concentrations of IGF-I in elderly men.[79-81] It has been suggested that the reduced growth hormone levels in the elderly may be responsible for changes in body composition.[82] Recently cross-sectional studies showed that basal serum IGF-I levels were negatively correlated with indices of adiposity, the percentage of body fat, and indices of upper body fat and positively related to the cardiorespiratory response to exercise and physical activity.[83,84] Although this suggests that lower growth hormone and IGF-I secretion may contribute to the development of obesity in older men, other factors such as altered physical activity, caloric intake, and gonadal function are also important. Based on these observations, Rudman and colleagues treated a group of healthy men aged 61 to 81 years with growth hormone.[85] Preliminary studies showed small (less than 10%) increases in lean body mass, decreases in adipose-tissue mass, and minimal increases in lumbar vertebral bone density (1.6%). Parfitt recently reviewed the effects of growth hormone on adult bone remodeling.[86] The studies indicate a parallel increase in markers of bone resorption and formation, suggesting the activation of bone remodeling but a questionable net change in bone density. The risk-benefit ratio for long-term growth hormone therapy in elderly men has not been established, nor has it been shown conclusively that increased adiposity and decreased muscle mass are directly related to growth hormone or IGF-I deficiency. The possible risks of growth hormone and IGF-I therapy may include osteoarthritis and neoplasia.[87] In prepubertal boys and hypogonadal men, treatment with testosterone or human chorionic gonadotropin increases mean growth hormone levels, pulse amplitude, and serum IGF-I levels.[88,89] The low IGF-I and changes in growth hormone levels in aging men may be related to the hypogonadism. This possibility has not yet been adequately explored.

Possible Adverse Effects of Androgen Replacement Therapy

Although androgen replacement therapy may have benefits on bone mass, muscle strength, and psychosexual and cognitive function in elderly men with low testosterone levels, adverse effects may occur.[90] Androgen therapy is associated with mild weight gain of a few kilograms. Gynecomastia as a result of androgen therapy is mild and requires no treatment. Excessive oiliness of the skin and the development of acne are seen in younger men given androgen replacement. Whether these skin changes will occur in elderly men is not known. These changes in the skin usually require no treatment or the external application of cleansing soap. Other side effects may occur, including the aggravation of prostatic disease, alterations in lipid and carbohydrate metabolism, sleep apnea, and increased erythropoiesis and fibrinolysis.

Prostatic Disorders

Prostatic diseases (cancer and benign prostatic hypertrophy) are common problems of elderly men. Neither of these conditions develops without testosterone exposure during puberty and early adulthood. There is no direct relationship between serum androgen levels in adult or elderly men and the incidence of these disorders. Androgens in in vitro experiments regulate programmed cell death of prostate cells. The adult prostate maintains its size through a balance between the processes of cell death and cell renewal. Androgens modulate growth and differentiation of the prostate directly or may interact with a number of growth factors, their receptors, and binding proteins within the prostate.

Prostate cancer is one of the most commonly diagnosed cancers in the United States. It occurs in a preclinical (microscopic) and a clinical form. By the seventh decade, about 50% of men have microscopic prostate cancer. But the progression of preclinical cancer to clinical prostate cancer occurs in only a small proportion of these men. The progression to clinical disease is variable among ethnic groups and is associated with environmental as well as genetic factors. There are no data to show whether androgen therapy will enhance the progression of preclinical to clinical cancer. Androgens are known to stimulate the growth of clinically diagnosed prostate cancer.[91]

Benign prostatic hypertrophy occurs in more than 80% of men aged 70 years or older. It leads to urinary outflow obstruction that usually requires surgical intervention. Recent studies have shown that decreasing the production of testosterone and dihydrotestosterone in men with benign prostatic hypertrophy decreases the prostate size and improves urinary flow.[92] Despite the theoretical considerations, there is no evidence that the replacement of androgens in hypogonadal young or elderly men will lead to the development of hyperplasia or aggravate its clinical status. Clearly, careful monitoring of prostate size and abnormalities by rectal examination and prostatic ultrasonography, urinary flow studies, and markers of prostatic disease such as prostate-specific antigen are required in elderly men treated with androgen replacement therapy.[90,93]

Lipid and Carbohydrate Metabolism

The relationship of circulating androgens to lipid profiles is somewhat controversial. Correlative studies have suggested that both testosterone and high-density lipoprotein (HDL)-cholesterol levels decline with age. Data in younger men have also shown a direct correlation between serum testosterone and HDL-cholesterol levels. These data have recently been reviewed and have led to the suggestion that testosterone treatment may raise HDL-cholesterol levels and be beneficial to patients with coronary artery disease.[94] On the other hand, synthetic 17α-alkylated steroids have been shown to decrease HDL-cholesterol and apoprotein A-I and A-II levels and to increase low-density lipoprotein (LDL)-cholesterol levels.[95] The importance of this finding is that low HDL

levels and high LDL-to-HDL ratios are associated with an increased risk for coronary artery disease. When androgens such as testosterone and its esters are given to hypogonadal or eugonadal men, small decreases or no significant effects on LDL-cholesterol and mild decreases in HDL-cholesterol levels are seen.[59,95-97] It has been postulated that the difference in the effect of 17α-alkylated androgens and testosterone on lipids is that testosterone is converted to estradiol (aromatizable androgens), which has an opposite effect from androgens on blood apoproteins and cholesterol levels. The clinical significance of a small decrease in HDL-cholesterol levels is unknown.

Testosterone does not cause glucose intolerance or increased insulin secretion. This is in contrast to the effects of 17α-alkylated androgens, which increase the insulin response to glucose and impair glucose tolerance in men.[98]

Sleep Apnea

Sleep apnea is much more common in men than in women. Obese men, elderly men, patients with chronic obstructive pulmonary disease, and patients with acromegaly are predisposed to sleep apnea. Administering androgen to hypogonadal young men can precipitate or aggravate clinical symptoms of sleep-related breathing disorders.[99] The administration of androgens to elderly men could be a problem, especially in those who are overweight, heavy smokers, or who have chronic obstructive airway disease.

Erythropoiesis and Fibrinolysis

Androgens increase red cell mass mainly through a direct effect on erythropoietin. Androgens also have a direct effect on the bone marrow stem cells. Adult men have higher hemoglobin concentrations than male children, hypogonadal men have lower than normal red cell mass, and correcting androgen deficiency leads to a substantial increase in hemoglobin levels—all of which demonstrate the relationship between androgens and erythropoiesis.[100] Administering androgen to normal men also increases their hematocrit and red cell mass.[101] Elderly men have lower hematocrits than younger men. Androgen replacement in elderly men will stimulate erythropoiesis and increase red cell mass. It is unknown, however, whether the androgen-induced increase in hematocrit is beneficial to the elderly men or may lead to more frequent episodes of thromboembolism.[102]

Administering anabolic17α-alkylated androgens such as stanozolol may increase fibrinolytic activity and antithrombin III (a natural anticoagulant) levels.[100] The increase in fibrinolytic activity may neutralize some of the effects of increased hematocrits and altered HDL-to-LDL ratios by decreasing intravascular clotting ability.[90]

Summary

Aging in men is generally accompanied by a decrease in testosterone levels and, in particular, free testosterone levels. Androgen substitution in elderly men with low testosterone levels has been shown in recent reports on small numbers of patients to improve sexual function and prevent bone loss. Large prospective placebo-controlled studies are required to confirm the beneficial effects of androgens on bone and muscle mass, physical well-being, and psychosexual function. These studies will also help to clarify whether androgen substitution may stimulate prostate growth, leading to prostate disease. The effects of androgens on lipid levels, hematocrit, fibrinolytic activity, and the respiratory system can be carefully monitored. These studies will give a risk-to-benefit ratio of androgen replacement therapy in elderly men and will be a prerequisite to the development of treatment strategies of aging men.

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Conferences and Reviews

Controversies in Patient Selection for Liver Transplantation

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A variety of specific conditions often stimulate controversy regarding candidacy for liver transplantation. We review the published experience with liver transplantation for alcoholic liver disease, fulminant and chronic hepatitis B, and hepatocellular carcinoma and transplantation in older subjects. Liver transplantation for alcoholic liver disease and in subjects older than 60 years is becoming less controversial because recent data demonstrate that these patients have excellent survival and good quality of life after transplantation. Only 10% to 15% of persons with alcoholism return to drinking after transplantation, and most do so only transiently. Liver transplantation for patients with hepatitis B virus infection or primary liver cancer is more problematic because recurrent disease is common in both conditions. After transplantation for chronic hepatitis B, 80% to 90% of patients have reinfection of the allograft and long-term survival is 45% to 50%. Patients receiving transplants for hepatocellular carcinoma have only 20% to 30% long-term survival, but these survivors are cured of malignancy. Data are presented to support continued liver transplantation for chronic hepatitis B and hepatocellular carcinoma; however, patients must be selected based on factors that predict a favorable outcome, and experimental therapies should be employed to explore ways to improve the existing survival rates.

(Keeffe EB, Esquivel CO: Controversies in patient selection for liver transplantation. West J Med 1993; 159:586-593)

Human orthotopic liver transplantation was initiated in 1963, but results were poor until the early 1980s when the one-year survival rate increased from approximately 30% to more than 60%.[1] Several factors, including the refinement of surgical techniques, improved perioperative care, more effective and safer immunosuppressive therapy, and better selection of patients, accounted for this remarkable increase in survival. In 1983 the treatment of end-stage liver disease with orthotopic liver transplantation was declared no longer experimental.[2] The survival of patients undergoing the procedure has improved progressively throughout the 1980s and early 1990s. Survival rates greater than 80% are now routine at transplant centers, as evidenced by 87% one-year survival and 85% two-year survival at California Pacific Medical Center (CPMC) during the first one to two years of the liver transplantation program.[3,4]

Over the past decade, the number of liver transplant operations and centers has grown dramatically. More than 100 centers are now operating in the United States, and approximately 3,000 liver transplantations were performed in 1992. This growth, fueled further in 1991 by the approval of Medicare funding for the operation, has resulted in an increase in the number of patients on transplant waiting lists and the number of deaths before transplantation can be achieved. These factors present many challenges for the future, including the refinement of patient selection criteria.[5] The merits of performing transplants in certain patient groups, specifically those with underlying diseases that may recur after the procedure, continue to be controversial.

The classic indications for orthotopic liver transplantation are advanced cirrhosis, fulminant hepatic failure, unresectable hepatic cancer, and metabolic liver disease.[1] These broad indications encompass nearly all types of liver disease. In addition, patients must have no alternative therapy, no contraindications to transplantation, and the ability to pay for the procedure and follow-up care. Absolute contraindications include the acquired immunodeficiency syndrome; primary hepatic malignancy spread beyond the liver; active and untreatable alcoholism or drug abuse; advanced extrahepatic disease, particularly cardiopulmonary conditions; and thrombosis of the splanchnic venous circulation (portal, splenic, and superior mesenteric veins).

Within these broad selection criteria for liver transplantation, controversy exists regarding whether patients with certain liver diseases should be approved for the procedure. For example, should patients with alcoholic cirrhosis, chronic hepatitis B, or primary liver cancer (hepatocellular carcinoma or cholangiocarcinoma) receive transplants? These three conditions share several features—in particular the possibility of recurrence and reduced long-term survival after transplantation—that

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ABBREVIATIONS USED IN TEXT

CPMC = California Pacific Medical Center
CT = computed tomographic
HBeAg = hepatitis B e antigen
HBIG = hepatitis B immune globulin
HBsAg = hepatitis B surface antigen
HBV = hepatitis B virus
HDV = hepatitis delta virus
TNM = tumor-node-metastasis

account in part for their controversial status. Because donor organs are in short supply and the number of deaths on the waiting list has increased, the argument is presented that donor organs might better be allocated to persons on the waiting list expected to have optimal initial and long-term survival. Another area that often stimulates debate regarding candidacy for the procedure is the presence of associated medical conditions that may adversely influence the outcome. For example, should patients who are older than age 60 receive transplants? These four areas of controversy will be reviewed.

Alcoholic Cirrhosis

Until the past few years, orthotopic liver transplantation was not considered a treatment option for patients with alcoholic liver disease. The initial experience with transplantation for these patients at several transplant centers demonstrated poor results, and there was concern that a high recidivism rate would substantially reduce long-term survival. In 1988, researchers from the University of Pittsburgh found that the survival of 42 patients who received transplants for alcoholic liver disease was not different from the survival of patients undergoing the procedure for other causes of cirrhosis.[6] Moreover, only 2 of 35 patients surviving more than six months returned to alcohol abuse.

Many compelling reasons exist for patients with alcoholic cirrhosis to be considered for liver transplantation. Alcoholic liver disease is prevalent and often fatal, with more than 30,000 liver-related deaths annually in the United States associated with alcoholism.[7] Alcoholic cirrhosis is the cause of more than half of the cases of end-stage liver disease in the United States. Patients undergoing transplantation for alcoholic cirrhosis are often younger than 50. Thus, the potential exists for long-term survival and a return to productivity in the home and workplace. Most important, the published survival data from several liver transplant centers have confirmed the findings of the 1988 University of Pittsburgh report and demonstrated that the long-term survival for patients with alcoholic cirrhosis after the procedure matches the survival of patients with other types of cirrhosis.[8-10] Finally, after transplantation the rate of recidivism is low, averaging 10% to 12%, and the rate of compliance with medical follow-up by patients with alcoholism is high.[9-11]

Liver transplant centers have applied different selection criteria for patients with alcoholic liver disease. The development of a rational and structured approach that predicts compliance and long-term sobriety in the post-transplantation period is critically important and has been reported by some centers.[9,10] A multidisciplinary team of medical, surgical, and psychiatric members contributes to pretransplant evaluation and the determination of suitability for transplantation. Investigators from the University of Michigan developed an "alcoholism prognosis scale" based on the acceptance of alcoholism by the patient and family, social functioning and stability, and changes in life-style such as substitute activities, social relationships, and hope and self-esteem.[9] Of all patients with alcoholic cirrhosis referred to the University of Michigan for liver transplantation, fewer than 50% were accepted.[9] The actuarial survival of those patients with alcoholism who received transplants was no different from that of the patients without alcoholism; both had survival of about 80%. Only a small number of alcoholic patients drank after receiving a transplant, and most of these only transiently. These investigators attributed their center's success with liver transplantation for alcoholic cirrhosis to the use of their alcoholism prognosis scale.

Using a slightly different but conceptually similar approach at CPMC, the results of transplantation for alcoholic cirrhosis have also been good with a 93% actuarial survival at 42 months.[10] Based on their psychosocial state and medical condition, referred patients with alcoholic liver disease are categorized by a standardized protocol into groups with low risk, moderate risk, and high risk for recidivism and noncompliance. Low-risk patients admit alcoholism, agree to participate in an alcohol treatment program, sign an alcohol treatment contract, have not failed treatment programs in the past, do not have major psychiatric disease, and are medically fit. These low-risk patients are placed on the waiting list for transplantation. High-risk patients have failed alcohol rehabilitation programs, deny their alcoholism, refuse to sign an alcohol contract, have major psychiatric disease, and have advanced coincidental medical problems or alcohol damage to organs other than the liver. These patients are turned down for the procedure. Moderate-risk patients fall between the high- and low-risk groups and are deferred for transplantation. These patients are observed by the referring physician and the transplant team while they participate in an alcohol treatment program; if they are compliant and remain abstinent, they are subsequently placed on the waiting list for the procedure. Follow-up results of the initial 47 patients entered into this prospective protocol have confirmed its predictive value. Of 31 low-risk patients, 27 received transplants; 5 of the 31 patients (16%) drank alcohol, but only transiently. Ten patients were classified as moderate risk and deferred, and two of these patients later received transplants; all ten patients either were noncompliant or drank alcohol. Of the six patients classified as high risk, five (83%) were noncompliant or drank alcohol. In fact, the actuarial survival of patients undergoing transplantation for alcoholic cirrhosis at CPMC is better than that of patients who receive transplants for other conditions at our institution (Figure 1).

The period of abstinence required to be considered for liver transplantation has changed dramatically in recent

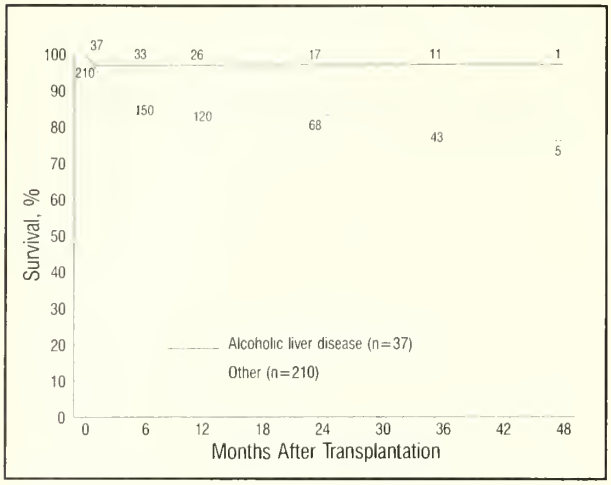

Figure 1.—The actuarial survival of patients undergoing orthotopic liver transplantation for alcoholic cirrhosis surpasses that of patients who receive transplants for other indications at California Pacific Medical Center.

years. Many transplant programs previously mandated six months of abstinence, but many patients died of liver failure during that arbitrary and fixed waiting period. Some period of abstinence is still an important consideration in predicting posttransplant sobriety, but it is no longer the sole determining factor and is considered along with other predictors of abstinence.[9,10] Because patients with acute alcoholic hepatitis are typically drinking alcohol up to or near the time of hospital admission, they are usually not offered transplantation.

In summary, alcoholic cirrhosis is becoming less of a controversial issue in patient selection for orthotopic liver transplantation, although the topic continues to be debated.[12-14] Medicare recently approved funding for liver transplantation for alcoholic cirrhosis, which has become the single leading indication for the procedure.[14] Alcoholic patients undergoing transplantation should have prognostic factors that predict long-term sobriety and compliance. Survival after the procedure is good (75% to 80%), and most patients (85% to 90%) remain abstinent from alcohol. It is important to note that, although results are currently encouraging, alcoholic patients receiving transplants are highly selected, and follow-up is still relatively short.

Fulminant and Chronic Hepatitis B

A second major area of controversy in selecting patients for orthotopic liver transplantation is whether to offer transplants to patients with hepatitis B virus (HBV) infection. Transplantation for fulminant hepatitis B is associated with good survival and outcome; many of these patients do not have recurrent HBV infection, possibly because a vigorous immune response clears the virus.[15-19] By contrast, the three- to five-year actuarial survival of patients receiving transplants for chronic hepatitis B is 45% to 50%, which is 25% lower than the expected survival after liver transplantation for other causes of end-stage cirrhosis.[1,15,16]

This reduced survival for patients with HBV infection is related to reinfection of the graft, which is often associated with accelerated liver disease and may evolve rapidly to graft failure in some patients.[15,16,20,21] Graft failure, characterized clinically by progressive hyperbilirubinemia and only a modest elevation of aminotransferase levels, has been called "fibrosing cholestatic hepatitis"[20] or "fibrosing cytolytic hepatitis."[21] The histologic findings include a ballooning degeneration of hepatocytes, periportal fibrosis, and a paucity of inflammatory infiltrates.[20,21] These features are accompanied by a prominent expression of hepatitis B surface antigen (HBsAg) and hepatitis B core antigen in most hepatocytes by immunohistochemical staining.[20-23] This enhanced expression of HBV proteins and the lack of significant histologic inflammatory response supports a cytopathogenic role for the virus in this disease after transplantation.[20,21] The precise mechanisms for this direct cytopathogenicity, in contrast to the usual immune pathogenesis of chronic hepatitis B in patients not receiving transplants, is unknown.

Recurrent HBV infection is associated with a broad disease spectrum ranging from an asymptomatic patient with histologic findings of mild focal hepatitis or chronic active hepatitis to a symptomatic patient with chronic active hepatitis with cirrhosis or fibrosing cytolytic hepatitis.[16,20] The recurrence of HBV infection follows the course of the original disease over a variable but accelerated time frame. Even primary hepatocellular carcinoma has been reported after transplantation for chronic hepatitis B.[24] Investigators from King's College in London have identified three phases of recurrent HBV infection after liver transplantation: an incubation phase during which HBsAg is not present or present at decreasing levels; an early infection phase during the first three months after the return of HBsAg positivity; and an established infection phase with a plateau of HBsAg titers and ongoing viral replication with hepatitis B e antigen (HBeAg) or HBV DNA seropositivity or both.[20]

The strongest predictor of the recurrence of HBV infection is the presence of HBV replication as defined by circulating HBeAg or HBV DNA.[16,17] Todo and colleagues reported that only patients who were HBeAg-negative before the transplantation cleared HBV after the procedure.[16] In the overall analysis of their experience, 8 of 30 HBeAg-negative patients cleared the virus, whereas none of 26 HBeAg-positive patients cleared HBsAg. This observation was confirmed by Samuel and associates, who found that patients with chronic hepatitis B with detectable serum HBV DNA had a much greater risk of HBsAg recurrence than patients who were HBV DNA-negative (96% versus 29% at two years).[17] In their institution, all patients received a hepatitis B immune globulin (HBIG) preparation, which reduced HBV reinfection and improved survival in patients without evidence of active HBV replication before transplantation when compared with other series and with their own institutional experience before the initiation of HBIG therapy.

Hepatitis B virus DNA was also an important marker of recurrent HBsAg in a treatment trial in Hannover, Ger-

many, where HBIG was used for patients who received transplants for chronic hepatitis B.[25] Recurrent HBV infection was prevented in only one of nine patients with HBV DNA, HBeAg, or both detected in serum before the transplant. By contrast, HBV recurrence was prevented in 10 of 14 HBV DNA–negative patients. These studies suggest that the degree of viral replication is the major determinant of the incidence and severity of recurrent HBV infection after liver transplantation. Immunosuppressive drugs may play a critical role in HBV replication after transplantation, based on the modulating effects of corticosteroids on HBV replication.[26]

Other factors may influence the recurrence of HBV infection after transplantation. The replication of HBV has been demonstrated in extrahepatic sites such as bone marrow, spleen, and pancreas.[27] Moreover, HBV has been found in peripheral blood mononuclear cells in the absence of hepatic infection after liver transplantation.[28] Another factor that may influence the recurrence of HBV infection is coexistent hepatitis delta virus (HDV) infection.[29-31] Superimposed HDV infection inhibits HBV replication and may enhance the clearance of HBsAg after transplantation. In the study of Todo and co-workers, four of eight anti-HDV–positive patients cleared HBsAg.[16] A survival rate of 78% was reported in 27 HDV-positive patients who received transplants in Italy and Belgium,[30] and 13 of 16 HDV-positive transplant recipients treated with HBIG in France have remained HBsAg-negative.[31]

In a review of the cumulative experience from the University of Pittsburgh with liver transplantation for fulminant and chronic hepatitis B, the long-term survival of transplant recipients surviving more than 60 days was 60% (23 of 38 patients), which is substantially less than the 80% survival reported in a control group receiving transplants for other causes of end-stage liver disease.[16] The actual survival, however, was only 45% of the original 51 patients transplanted for chronic hepatitis B. In contrast, seven of eight patients who received transplants for fulminant hepatitis B survived more than 60 days. One patient cleared HBsAg, and five of the surviving seven had no serious hepatic dysfunction. The treatment of HBV infection was attempted with active and passive immunization. Of 22 patients treated with this regimen and surviving more than 60 days, 6 cleared HBsAg.

At CPMC, 17 patients underwent 19 liver transplant operations for chronic hepatitis B and 5 patients had 6 transplantations for fulminant hepatitis B. The actuarial survival of the 17 patients receiving transplants for chronic hepatitis B was 78%, and all patients receiving transplants for fulminant hepatitis B are alive (Figure 2). Five of seven patients receiving HBIG for three to six months are HBsAg- and HBV DNA-negative; two of these five patients are also anti-HDV–positive. Three of the five patients (60%) receiving transplants for fulminant hepatitis B have recurrent HBV infection.

Various medical therapies have been used singly or in combination to prevent or treat recurrent HBV infection in transplant recipients. Hepatitis B immune globulin appears to show the greatest promise, but data regarding its

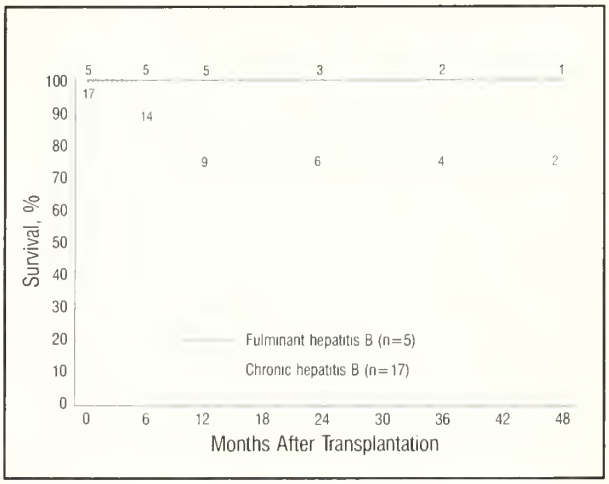

Figure 2.—The actuarial survival of patients undergoing orthotopic liver transplantation for chronic hepatitis B and fulminant hepatitis B at California Pacific Medical Center is shown.

efficacy are conflicting. Moreover, HBIG therapy has a high cost that is typically not reimbursed by insurance programs in the United States. In addition, the commercial products used in Europe may have a different efficacy and side effects compared with the US product, and the US product is not marketed for intravenous use. In research protocols, HBIG is typically given for varying time periods (3 months to 2 years) in intravenous or intramuscular doses to maintain anti-HBs levels greater than 100 units per liter. A French group treated 110 HBsAg-positive patients with long-term HBIG for as long as two years and found that HBsAg reappeared in only 22.7%.[17] The overall two-year actuarial recurrence of HBsAg was 59% after transplantation for chronic hepatitis B, 13% after transplantation for chronic hepatitis B with HDV coinfection, and 0% after the procedure for fulminant hepatitis B. The recurrence rate of HBsAg was 96% in patients with chronic hepatitis B and serum HBV DNA before transplantation versus 29% in those without HBV DNA. In the Hannover study, the infection did not recur in more than 80% of 23 patients treated with long-term HBIG therapy.[25] Reinfection developed in only a minority of patients who were HBV DNA-negative but in all patients who were HBV DNA-positive. At CPMC five of seven patients receiving HBIG for three to six months remain HBsAg- and HBV DNA-negative. In contrast, a recent preliminary report from the University of Nebraska Medical Center found that the use of HBIG was not effective and that only 2 of 11 patients survived long term after transplantation.[32]

Other medical therapies that have been used to prevent or treat HBV reinfection after liver transplantation have not been successful. Active immunization with HBV vaccine and interferon alfa have not been efficacious.[16,33] The use of monoclonal antibodies against HBsAg, rather than the standard polyclonal HBIG, is being studied to determine if this approach will produce higher titers of anti-HBs and less HBV reinfection.[34] Ganciclovir has been reported in preliminary studies to temporarily decrease

serum HBV DNA in patients with chronic hepatitis B after kidney and liver transplantation.[35] The practicality and long-term results of this approach remain uncertain. What is needed is an effective antiviral agent that will eradicate HBV.

In summary, the current approach of many transplant centers is to offer liver transplantation to patients with fulminant and chronic hepatitis B and liver failure, but only when they are entered into an experimental protocol, such as therapy with HBIG. Some centers perform transplantation on patients with chronic hepatitis B only if they are HBV DNA-negative or HBeAg-negative or both. Enough patients survive and return to productive lives to justify the continued use of transplantation for chronic hepatitis B. Unfortunately, patients with end-stage liver disease and HBsAg positivity are excluded by Medicare, some state Medicaid programs, and some private insurance programs from coverage for this procedure. If HBIG or other experimental therapies can reduce or delay HBV reinfection or ameliorate the expression of hepatitis B in the allograft, then even more patients may be able to survive until a specific antiviral agent can be found that permanently suppresses or eradicates HBV.

Another possible alternative is xenotransplantation, as recently demonstrated by the short-term successful transplantation of a baboon liver into a patient with end-stage chronic hepatitis B.[36] This approach is experimental and requires broader study, but xenotransplantation may have particular application in patients with advanced chronic hepatitis B because the baboon liver is resistant to HBV infection.

Hepatocellular Carcinoma

The third major controversial issue of patient selection for orthotopic liver transplantation is primary hepatic carcinoma that is confined to the liver and cannot be resected. In this article, we will focus on hepatocellular carcinoma and will not discuss cholangiocarcinoma, which nearly always recurs, or other benign and malignant tumors of the liver.

Fibrolamellar hepatocellular carcinoma is a clinicopathologic variant that has a more favorable outcome. Pathologists can recognize this variant on the basis of unique histologic features, particularly bands of fibrous tissue. In general, it grows more slowly than other hepatocellular carcinomas and has a high resectability rate.[37,38] Compared with patients who had other liver cancers (n = 64), patients with fibrolamellar hepatic carcinoma (n = 12) who underwent subtotal hepatic resection at the University of Pittsburgh had a significantly better survival rate at 5 years (64.8% versus 26.3%).[38] On the other hand, the five-year survival rate of patients with standard and fibrolamellar hepatocellular carcinoma was not different after transplantation (37.5% versus 36.5%).[38] The rest of this review will focus on nonfibrolamellar hepatocellular carcinoma.

The selection of patients with hepatic cancer for transplantation is dependent on several factors. The malignant lesion must be confined to the liver as documented preoperatively by abdominal, pelvic, and chest computed tomographic (CT) scans and a bone scan. A specific indication for transplantation in patients with hepatocellular carcinoma is poor hepatic function due to coexistent advanced cirrhosis. As a final step, the transplant surgeon carefully explores the abdominal cavity for metastases before proceeding. Occasionally a back-up potential recipient will be brought to the transplant center in case metastases are found so that the organ can be given to another patient.

Hepatocellular carcinoma may present as a mass lesion that is found either because of symptoms or as an incidental lesion identified after transplantation by the pathologist in the explant. These incidental tumors are small, typically 3 cm or less in diameter. Patients with incidental hepatic carcinoma have a survival rate that is no different after the procedure from that of patients with cirrhosis alone. In the University of Pittsburgh series, the mean survival of patients undergoing transplantation who had malignant lesions smaller than 2 cm was 76.4 months versus 40.4 months for those with tumors larger than 2 cm.[38]

Data from several transplant centers indicate that several risk factors predict recurrent hepatocellular carcinoma. These include lymph node involvement, gross vascular invasion as seen by angiography or CT scan, microscopic invasion of blood vessels in the specimen, tumor size greater than 5 cm, multiple lesions, the presence of an infiltrating rather than a circumscribed lesion, and involvement of more than one lobe.[38,39] In a recent study of tumor doubling time of recurrent hepatocellular carcinoma after transplantation and after hepatic resection, tumors grew at a significantly faster rate when they recurred after transplantation.[40] This accelerated growth rate may be related to the consequences of immunosuppression with inhibition of host immunity against micrometastases.[40]

The likelihood of tumor recurrence after transplantation has led researchers to analyze the role of partial or subtotal hepatic resection compared with transplantation. Retrospective analysis of data from patients with hepatocellular carcinoma who underwent either hepatic resection or transplantation showed similar survival rates of as long as five years. The key factor in predicting recurrence was the tumor-node-metastasis (TNM) staging. Patients with cirrhosis had better survival after transplantation than after resection because considerable hepatic morbidity and mortality were associated with the resection of lesions in a cirrhotic liver. Patients with fibrolamellar disease and early tumor stages had the best survival.

The one- to five-year survival rates of patients receiving transplants for primary hepatic carcinoma at selected large transplant centers are displayed in Table 1.[38,39,41-43] The three- and five-year survival rates vary from approximately 15% to 40%. Selection factors appear to be critical, and improved survival can be predicted by standard TNM staging.[38,39] A particular problem for patients with hepatocellular carcinoma is difficulty in procuring a donor liver quickly based on the current policies of the United Network for Organ Sharing, which allocates liv-

TABLE 1.—*Survival After Orthotopic Liver Transplantation for Hepatocellular Carcinoma at Representative Large Liver Transplant Centers*

Center	Reference	Patients, No.	Survival, % 1-yr	2-yr	3-yr	5-yr
University of Pittsburgh	Iwatsuki et al[38]	105	65.7	49.0	39.2	35.6
Medizinische Hochschule	Ringe et al[39]	61	37.7	26.7	15.2	15.2
King's College Hospital	O'Grady et al[41]	50	42.5* 48.5†	37.3* 38.3†	--	--
New England Deaconess	Haug et al[42]	24	71.0	56.0	42.0	--
University of California, Los Angeles	Olthoff et al[43]	16	40.4	22.5	--	--

*Patients with hepatocellular carcinoma and cirrhosis.
†Patients with hepatocellular carcinoma but no cirrhosis.

ers to patients who are most ill with liver failure and have been on the waiting list the longest. Patients with hepatocellular carcinoma may need to wait six months or longer for a transplant.

Several adjuvant therapies are available for hepatic carcinoma, particularly when the tumors are small and few in number.[44] These therapies, including doxorubicin hydrochloride given before, during, or after the procedure[45] and pretransplantation chemoembolization—selective embolization of the feeding artery with gelatin sponge particles soaked in solutions of doxorubicin, mitomycin, and cisplatin[46]—show promise in improving the results of liver transplantation alone for hepatocellular carcinoma.

In summary, the optimal treatment of primary hepatic carcinoma would appear to be partial hepatic resection if a single tumor is present in a noncirrhotic liver in a location amenable to safe resection. The only option for patients with tumors unresectable by conventional surgical techniques and hepatocellular carcinoma that occurs with cirrhosis and poor hepatic function is orthotopic liver transplantation. Long-term survival is only 20% to 30%, which mandates that only patients having a favorable TNM staging and receiving some form of adjuvant chemotherapy should undergo the procedure.

Older Age and Liver Transplantation

Until the early 1980s, the usual accepted age limit for liver transplant candidates was 50 years. Although a report of US liver transplant survival data suggests that older patients have reduced survival,[47] analysis of data from nearly all large centers does not support this general conclusion. Data compiled over the past several years from the University of Pittsburgh show that patients older than 60 account for almost 11% of patients receiving transplants.[48] The survival of this group of patients, which included 156 recipients, is virtually identical with the survival of adults younger than 60.[48] Most of these older patients recovered fully with good functional status and without major symptoms. Of the survivors, 66.7% were fully functional and 27.3% were functional with some limitation; only 6% were partially or completely disabled.[48] The number of patients older than 60 years undergoing liver transplantation is increasing out of proportion to the number of younger patients receiving transplants. The approval of Medicare funding for the procedure should further increase the percentage of patients older than 60 years who have transplantation.

Data from the University of Nebraska are similar to those from the University of Pittsburgh and demonstrate that survival in patients older than 60 is the same as for those younger than 60.[49] When investigators in Nebraska analyzed their older patients according to their risk of dying of liver disease,[50] some important findings were seen in their senior recipients. Low-risk older patients had a survival rate that was essentially identical to that of younger adults—17 of 18 patients.[49] On the other hand, among 15 older patients who were at medium risk, one-year survival dropped to 60%. Those elderly patients who were at highest risk had only 30% one-year survival. These findings suggest that medically high-risk older patients might be excluded from transplantation, even though a small percentage had good survival.

The results of transplantation at the University of Wisconsin Medical Center in patients older than 60 years are also encouraging. The actuarial survival was 83% at two years, compared with 76% for recipients younger than 60 years.[51] At CPMC, the actuarial survival of 38 patients

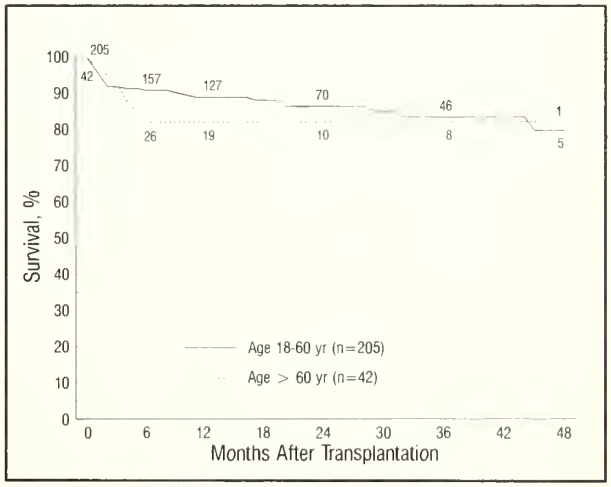

Figure 3.—The actuarial survival of patients older than 60 years who undergo transplantation is similar to that of adults between ages 18 and 60 receiving transplants.

older than 60 years is not different from the survival of all other adult patients (Figure 3). Thus, results from several centers demonstrate that older subjects generally do well after transplantation.

The incidence of acute rejection may be lower in older patients, and age itself may induce a degree of immunosuppression that explains the lower incidence of rejection.[48] Lower doses of immunosuppressive drugs may be appropriate in the elderly. In particular, the dosage of corticosteroids should be minimized to reduce the risk of problems such as diabetes mellitus, cataracts, and osteopenia.

In summary, survival rates after liver transplantation for patients older than age 60 are not different at one or three years from those of younger adults undergoing the same procedure. These results likely reflect the stringent selection and evaluation process that identifies older patients free of cardiac, pulmonary, and vascular disease. The primary concern in patient selection among the elderly is high-risk patients with advanced liver disease, who have poor survival. Thus, early referral is even more important in this age group.

Conclusions

Our recommendations regarding orthotopic liver transplantation for the controversial patient indications reviewed are as follows:

- Alcoholic liver disease: Offer transplantation to patients with good prognostic factors for sobriety and compliance;
- Chronic hepatitis B: Transplantation only in the setting of an experimental protocol, such as HBIG therapy that shows promise in reducing HBV reinfection, and possibly only for patients who are HBeAg- and HBV DNA-negative;
- Primary liver cancer: Offer the procedure only for the few patients who cannot have their hepatocellular carcinoma resected, have favorable TNM staging, and participate in an experimental protocol such as adjuvant chemotherapy or chemoembolization; and
- Patients older than age 60: Transplantation is acceptable, except possibly excluding high-risk patients with far advanced liver disease who have substantially reduced survival.

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* * *

STROKE

Furious, frantic, downed as a flash-flooded
oak, her left hand didn't wither, but dropped
in a second all its green leaves,
her left leg shriveled to a seeming-useless wire,
worthless as a severed root—

hope dried like cracked vines in an old, old
Italian garden, crookedly weaving between toppled
statues of children, young women, staring
at dirt, not daring to wish for rain, wind
or the next day, or any day—

but pith-deep in this woman, iron, water
mixed to explode, pushed sap back through
kinked, flaking canals of brain,
refueled stuttering cell fires—

and after weeks of sun and dark,
low-banked steady fury,
her hand undulates in the light,
she steps again with a walker down the street.

RON LINDER, MD©
San Francisco, California

Epitomes

Important Advances in Clinical Medicine

Emergency Medicine

The Council on Scientific Affairs of the California Medical Association presents the following inventory of items of progress in emergency medicine. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome, and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, researchers, and scholars to stay abreast of these items of progress in emergency medicine that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Emergency Medicine of the California Medical Association, and the summaries were prepared under its direction.

Reprint requests to Division of Scientific and Educational Activities,
California Medical Association, PO Box 7690, San Francisco, CA 94120-7690

Ultrasonography in Blunt Abdominal Trauma

In patients with blunt abdominal trauma, ultrasonography offers the advantage of immediate bedside availability; it is also noninvasive, safe, and inexpensive. As no radiation, contrast agent, or sedation is needed, ultrasonography can especially help with the care of pregnant or pediatric patients. Patients with allergies to contrast media or previous laparotomies in whom diagnostic peritoneal lavage could be difficult may also benefit.

Ultrasonography can detect intraperitoneal fluid collections as small as 100 ml, but cannot distinguish blood (hemoperitoneum) from other fluid (ascites). Subhepatic, perirenal, and subphrenic fluid collections can be evaluated, as can injury to the solid organs themselves. The visualization of free fluid in Morrison's pouch, between the liver and the right kidney, has been considered a criterion for laparotomy in some clinical series.

Hemoperitoneum and parenchymal damage can be diagnosed by emergency department sonograms with specificity and sensitivity of more than 90%. When its use is directly compared with that of diagnostic peritoneal lavage, however, several studies have shown that ultrasonography is not as sensitive or accurate. It is the initial imaging procedure for blunt abdominal trauma in many European centers, with workup proceeding to diagnostic peritoneal lavage, computed tomography, intravenous pyelography, scintigraphy, or other studies only secondarily.

Limitations on the use of sonograms include the presence of subcutaneous emphysema or ileus where air may obscure the image. Injuries to the pancreas and to hollow viscus, particularly the duodenum, are not reliably diagnosed. Further, scan quality and the accuracy of interpretation are dependent on operator skill and experience. Whereas in many studies scans are done by surgical residents, a few authors advocate that a radiologist do the study, even in an emergency department.

Ultrasonography is complementary to diagnostic peritoneal lavage or computed tomography. When used to supplement, but not supplant, these diagnostic modalities, it may add speed and flexibility to answering the question—is laparotomy needed?—in patients with blunt abdominal trauma.

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Flumazenil—When Is Its Use Appropriate?

Flumazenil is a competitive benzodiazepine antagonist that, when released in 1992, was heralded as a possible panacea for complications associated with the use of benzodiazepines. In fact, this drug is useful in patients with benzodiazepine overdose. Its efficacy is more limited in patients with mixed overdoses or in those with an altered mental state of unknown cause, and its role in the reversal of conscious sedation has proved to be controversial.

The action of flumazenil is dependent on both the dose of the benzodiazepine being antagonized and the dose of the flumazenil used. The half-life of flumazenil usually ranges from one to two hours and is shorter than that of most benzodiazepines. This difference in half-life raises the possibility of resedation after the flumazenil wears off; the clinical importance of this prospect varies depending on the situation.

Flumazenil's main clinical role is in patients with either iatrogenic or intentional benzodiazepine overdose. In patients with pure benzodiazepine overdose, 95% awaken

within five minutes of receiving doses of flumazenil totaling 0.2 to 1.0 mg intravenously; some patients require doses of as much as 5.0 mg. Although in many patients the use of flumazenil eliminates the need for intubation, the reversal of respiratory depression may be inadequate, particularly in patients with mixed overdoses (such as with opioids and benzodiazepines). It is also important to note that resedation may occur, especially in patients who receive or ingest large amounts of benzodiazepines. These patients need to be watched closely and may require repeated doses of flumazenil or a continuous infusion of 0.5 to 1.0 mg per hour.

Using flumazenil to reverse conscious sedation is controversial. In emergency departments, conscious sedation is often used during procedures that are uncomfortable and stressful for the patient. The sedative and anxiolytic effects of benzodiazepines are desirable in these patients, and when specific drugs are chosen carefully, excessive sedation and respiratory depression are avoided. Although flumazenil rapidly reverses the sedative effects of benzodiazepines in these patients, its use may be neither necessary nor beneficial. In addition, although patients are more awake after receiving flumazenil, it is not clear that they fully recover their cognitive functions; using it to hasten a patient's discharge may be inappropriate. These patients should be observed until the effect of the benzodiazepine wears off.

The initial dose of flumazenil in most patients is 0.2 mg intravenously over 15 to 30 seconds; an additional 0.3 mg over 10 to 30 seconds should be given if there is no response after 30 seconds. If there is still no response, and the patient is being reversed from conscious sedation, doses of 0.2 mg should be repeated at 60-second intervals to a total of 1.0 mg. If the patient has a possible benzodiazepine overdose, flumazenil should be given in doses of 0.5 mg intravenously over 30 seconds every 60 seconds to a total dose of 3.0 to 5.0 mg. If these patients do not respond to the maximal dose, another cause of their altered mental state should be sought.

Complications associated with the use of flumazenil are not due to the flumazenil per se, but to the loss of benzodiazepine effect. Dizziness, anxiety, agitation, and gastrointestinal symptoms may occur and are usually mild. Seizures, a more serious complication, may occur when the drug is used in patients who are benzodiazepine-dependent. In addition, the use of flumazenil in patients who have ingested medications that may cause seizures, such as tricyclic antidepressants, isoniazid, cocaine, and propoxyphene, may block the therapeutic anticonvulsant effect of benzodiazepines if their use is needed. The use of flumazenil should be avoided in patients suspected to fall into this group of patients.

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Stabilizing and Resuscitating Patients With Automatic Implantable Cardioverter-Defibrillators

As AUTOMATIC IMPLANTABLE cardioverter-defibrillators (AICDs) are increasingly used in patients with recurrent malignant ventricular arrhythmias, the likelihood of a patient presenting with problems relating to their AICD is increasing. Physicians must be aware of the basic functioning of AICDs and the management of emergent problems relating to them.

The AICD pulse generator is a computerized device that is usually implanted into the abdominal wall. Leads are placed on or in the heart to sense cardiac activity and to conduct the impulses from the pulse generator. The primary purpose of the AICD is to deliver a countershock to the heart in response to malignant tachyarrhythmias. The most common devices trigger their countershocks based on the sensed ventricular rate (technically, the RR interval). They cannot differentiate between supraventricular and ventricular tachycardias. The newer generations, with waveform-sensing functions, should include this capability.

Patients may come to an emergency department with a limited number of acute AICD-related problems. The most serious is ventricular tachycardia or fibrillation, which necessitates cardiopulmonary resuscitation following current advanced cardiac life-support guidelines. There is no risk to the resuscitation team from the device; it can, however, interfere with the resuscitation substantially and should be deactivated.

An AICD is deactivated by placing a standard ring-shaped pacemaker magnet over the upper right corner of the pulse generator. This may be somewhat difficult to ascertain because the generator may have turned or may have been implanted upside down. Clues are that the AICD is somewhat narrower and the leads issue from the top. When the magnet is properly applied, the generator should make tones or beep in synchrony with the QRS complex. It may emit double tones if it is also sensing the T wave. The magnet should be left on a minimum of 30 seconds, and the tone will change to a long, continuous one. This indicates that the AICD is deactivated. The magnet may then be removed, and the AICD will remain deactivated. If the AICD does not beep when the magnet is placed, it should be placed over the other corners of the device. Once the AICD is deactivated, standard resuscitation measures may then proceed.

Patients may also have symptoms relating to arrhythmias, such as palpitations, syncope, or dizziness, but with no apparent function by the AICD. When evaluating a patient, full cardiac resuscitation equipment including a defibrillator should be immediately available. The basic

sensing and operation of the AICD may be checked again with the magnet. If the device does not sound with each QRS complex, it is either dead or not sensing correctly. Even if the AICD sounds with the magnet, patients with serious symptoms attributable to arrhythmias should be evaluated and admitted to an intensive care area with specialty consultation.

Another scenario involves patients who receive a shock from their device. This may be either an appropriate shock, indicating that the patient has survived an otherwise-lethal arrhythmia, or an inappropriate shock due to device malfunction or supraventricular tachycardia. If the patient presents after a shock, but otherwise looks well, it can be assumed that the shock was an appropriate one. Patients should be fully monitored, antiarrhythmic levels measured, and a specialty consultation obtained immediately. Usually these patients must be admitted to a monitored bed, but selected patients, in consultation with their cardiologist, may be discharged. In all such cases, caution should be the guide.

Patients receiving obviously inappropriate shocks can be terror-stricken. Cardiac resuscitation equipment, including a defibrillator, must be at the bedside during evaluation. If the discharges are in response to a supraventricular tachycardia, the causes, such as uncontrolled atrial fibrillation, congestive heart failure, or ischemia, should be treated.

If the device is obviously malfunctioning or if the patient cannot tolerate the discharges until the supraventricular arrhythmia is controlled, the AICD may be deactivated with a magnet as described above. Extremely close monitoring, bedside resuscitation equipment including defibrillator, and immediate consultation are mandatory with any patient who has had their AICD deactivated. Admission to an intensive care area is mandatory.

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Options for Sedating Children

PEDIATRIC SEDATION has been the subject of much attention and controversy over the past several years. Despite recent advances, there is still no consensus on the best approach for safely and effectively sedating children in an emergency department.

The most commonly used sedative preparations for pediatric patients are chloral hydrate and the combination of meperidine hydrochloride, promethazine hydrochloride, and chlorpromazine. Chloral hydrate is a sedative hypnotic with a long record of safety and efficacy. Sedative doses produce somnolence with little effect on respiration or blood pressure. It is especially useful for young children having procedures such as computed tomography, magnetic resonance imaging, or electroencephalography. Chloral hydrate has no analgesic properties and is therefore not generally used alone for painful procedures. Sedation occurs within 30 to 60 minutes at doses of 25 to 100 mg per kg orally or per rectum. Sedation is inadequate in 30% to 40% of patients, and additional doses are often needed. Complications are rare; the most common are gastric irritation and hyperactivity. There has been concern recently about possible toxicity. Chloral hydrate is a metabolite of an extremely toxic carcinogen, trichloroethylene. Carcinogenicity associated with chloral hydrate administration has not been described in humans. The United States Food and Drug Administration is currently conducting studies to investigate this possibility, and many practitioners have curtailed their use of chloral hydrate pending additional information.

The use of meperidine, promethazine, and chlorpromazine, a sedative analgesic combination, is familiar to many emergency department physicians. It is usually reserved for painful procedures such as fracture reduction or the repair of complex lacerations. Its use has been associated with a high incidence of adverse side effects, including respiratory depression, hypoxemia, and prolonged sedation. Overall, the efficacy and safety profile of this combination is poor compared with alternatives.

Midazolam hydrochloride is a newer benzodiazepine with sedative, anxiolytic, and amnestic properties. It has a rapid onset and short duration of action, making it particularly well suited for use in the emergency department. It has gained widespread popularity as a sedative for children undergoing radiographic studies, although some practitioners report high failure rates. Because of its lack of analgesic effect, it is not recommended as the sole agent for minor surgical procedures. It can be used successfully for short painful procedures because it has amnestic properties. Sedative doses minimally depress respiration and cardiovascular function, but respiratory depression and hypotension can occur. Midazolam is available only in parenteral form. The parenteral preparation can be given orally at a dose of 0.5 mg per kg; its bitter taste can be masked by mixing with soft drinks, juice crystals, or acetaminophen elixir. The intranasal route is preferred for infants. The dose for this is 0.3 mg per kg, and it may be dripped into the nose with a small syringe. Rectal midazolam is used less frequently. The standard parenteral form can be administered through a syringe connected to a gel-lubricated pediatric feeding tube inserted into the rectum at a dose of 0.3 mg per kg.

Pentobarbital sodium is used commonly for radiographic procedures. The barbiturates are sedative hypnotics with no analgesic action. Sleep doses in children, unlike in adults, rarely result in apnea, but hypotension can occur. Careful patient selection and monitoring are required. The dose for pentobarbital intravenously or intramuscularly is 2 to 6 mg per kg. Methohexital sodium and thiopental sodium are other barbiturates that have been used successfully in pediatric radiology. Methohexital, 10 mg per kg intramuscularly, and thiopental, 25 to 45 mg per kg per rectum, are the most common regimens.

Ketamine hydrochloride, a derivative of phencyclidine (PCP), has been used for many years in anesthesia. It provides a unique combination of sedation, analgesia, and amnesia, along with a "dissociated effect." Patients typically have a disconnected stare with stiffness, drooling, and nystagmus. There may be vomiting on awakening.

The use of potent sedatives in the emergency department mandates that proper safety mechanisms are in place. Physicians must have extensive knowledge of the medications and techniques used, be skilled in airway management, and be able to handle any complications that may arise. Specific guidelines for monitoring, equipment, and support personnel have been outlined by the American Academy of Pediatrics. Additional studies are needed to provide further information on the safe and efficacious use of sedatives in children.

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Dealing With Violence in the Prehospital Setting

THE CRISIS OF ESCALATING violence in society has resulted in emergency medical service (EMS) systems adapting and implementing changes in the delivery of medical care in prehospital settings. Rescuer safety has become a primary consideration to prevent a violent situation that turns rescuers into additional patients. These precautions may conflict with the public's expectation of immediate response by public safety agencies. Emergency medical service personnel holding back until the scene is "secure" may be perceived by the media and public as lacking in caring resulting in an unnecessary delay in the delivery of care. Nonetheless, EMS systems are adapting to the environment of increasing violence with design changes.

Modifications in the dispatching of EMS teams include the concurrent dispatching of law enforcement on calls associated with a high risk of violence—gunshot wounds, suicide attempts—and dispatching recognition and notification to the EMS personnel of addresses or areas previously associated with violence. Where possible, EMS crews should avoid traveling through dangerous areas during their response to calls.

In high-risk situations, EMS crews often "stage" at a nearby safe location until the scene is cleared by law enforcement officials. Although an increasing number of prehospital care professionals are wearing body armor (bullet-resistant vests), this protection is not a substitute for avoiding a violent situation and for common sense. Many EMS systems have recognized the similarity of prehospital professionals' uniforms to those of law enforcement officers (with badges and leather holsters worn on the hip) and are taking steps to modify the appearance of the EMS personnel to reduce the risk of misidentification.

Prehospital health care providers try to maintain a high level of awareness of their surroundings, looking out for any weapons or objects that could possibly be used as weapons. They maintain an adequate distance for their personal safety until the stability of the situation is assessed. Crews must clearly identify themselves as EMS personnel. As prehospital personnel approach a patient, they are careful not to encroach on the person's personal space before establishing rapport with the patient. A route of exit from any situation is considered, and personnel become aware of who and what is behind them.

Only in the absence of an adequate number of law enforcement officers should EMS personnel be involved in physically restraining a patient. Careful planning for the act of restraining the patient is necessary to avoid injury to EMS personnel or the patient. Pharmacologic approaches to restraint, such as the use of haloperidol, are in most cases not within the approved scope of practice for prehospital personnel. If the risk of violence is high enough to make the scene unsafe, EMS personnel retreat to safety and, if possible, remove the patient from that situation, initiating therapy in a safer environment.

Emergency medical service systems have recognized and are beginning to deal with the high tension associated with a violent work environment. Postevent stress debriefing should be given to personnel involved in a violent prehospital situation. Systems must recognize the inherent risks of burnout of personnel, spousal and family dissatisfaction with a career perceived as exceedingly dangerous, and the potential of substantial staff turnover.

An increased awareness of and planning for the possibility of violence at both an individual prehospital care provider and an EMS systemwide level are the best prophylaxis against violence resulting in death or injury to prehospital personnel.

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Sumatriptan—A New Treatment of Migraine

IN THE UNITED STATES an estimated 18% of the adult female and 6% of the adult male population suffer from migraine headaches. Current therapies using simple analgesics, such as nonsteroidal anti-inflammatory drugs, ergot alkaloids, antiemetics, and narcotic analgesics, have side effects and limited effectiveness. Sumatriptan (Imitrex, Glaxo Inc), a serotonin (5-hydroxytryptamine)-

receptor agonist recently approved in the United States for the treatment of acute migraine, may make these agents obsolete.

Sumatriptan is thought to relieve the pain of migraine by its direct action on a subgroup of serotonin receptors (5-hydroxytryptamine-1) in the walls of large intracranial arteries. By selectively activating serotonin receptors, sumatriptan causes vasoconstriction, thereby relieving migraine pain, which is thought to be due to vasodilation. Because sumatriptan is a selective receptor-specific agonist, it has fewer effects on the coronary and peripheral circulation than other antimigraine drugs, such as ergotamines, which are nonselective in their actions.

Studies comparing sumatriptan with placebo show that both subcutaneous and oral formulations are successful in relieving moderate to severe migraine in two hours in about 55% of patients following the oral administration of 100 mg and within an hour in about 75% of patients following a 6-mg subcutaneous dose. This compares to a placebo response of 15% to 20%. Patients not responding to a first dose of sumatriptan rarely benefit from a second dose, although the manufacturer recommends trying a second treatment. Sumatriptan is also effective in aborting the associated symptoms of nausea, vomiting, photophobia, and intolerance to noise. The drug is effective in both classic and common migraines, regardless of the time it is administered during the attack.

As many as 40% of patients who initially respond to sumatriptan have recurrent headache within 24 hours. This may be related to the short (2-hour) half-life of the drug. Whether these headaches can be prevented by repeated oral dosing has not been studied. Tachyphylaxis has not been shown to occur.

As many as half the patients treated with sumatriptan have an adverse event compared with a third of patients receiving placebo. These side effects are usually minor and resolve within 30 minutes. The most common side effects are burning, pain, and redness at the site of the injection and generalized flushing, tingling, warmth, or lightheadedness. Chest tightness is occasionally reported, but no association between chest complaints and electrocardiographic changes has been found. Nonetheless, sumatriptan is not recommended in patients with ischemic heart disease, Prinzmetal's angina, or uncontrolled hypertension or in patients taking lithium carbonate or 5-hydroxytryptamine reuptake-inhibitor antidepressants. The drug's safety has not been established in pregnant women or in children. The manufacturer of sumatriptan recommends not using ergotamine and sumatriptan within 24 hours of each other as their vasospastic effects may be additive.

Sumatriptan has undergone extensive worldwide clinical trials in the treatment of acute migraine and is now available in the United States as a 6-mg subcutaneous injection and as an autoinjector with prefilled syringes for subcutaneous self-administration by patients at home. The early use of this device at home has the potential for substantially decreasing the number of visits to emergency departments for migraine. It is anticipated that the oral form, already being used in Europe, will be available in the United States within a year. The wholesale price to hospitals is $26.50 per 6-mg dose. A starter kit with the autoinjector device and two prefilled syringes costs $56.80.

Although further clinical studies comparing the use of sumatriptan with that of existing migraine treatment regimens are needed and cost must be considered, sumatriptan has been shown to be a rapid, effective, well-tolerated treatment of migraine, and it is an important addition to the therapies currently available.

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Intravenous Diltiazem Hydrochloride Rather Than Verapamil for Resistant Paroxysmal Supraventricular Tachycardia

SUPRAVENTRICULAR TACHYCARDIA is a relatively common problem seen by physicians. Verapamil has been the medication of choice in treating stable patients with narrow-complex supraventricular tachycardia. Relatively recently, adenosine has become the first-line medication, predominantly because of its relatively short half-life and extremely safe drug profile. Many, if not most, physicians now start treatment with adenosine both diagnostically and therapeutically, but go back to giving verapamil to patients with resistant or recurrent tachycardia.

Verapamil, although a good medication for the disorder, is not free of complications. The most often quoted and feared complication is hypotension, especially in patients with already compromised circulatory function. Hypotension is thought to be due to the drug's direct cardiodepressant effects in addition to its smooth muscle vasodilatory effects. Some authors go so far as to recommend pretreatment with calcium chloride or, if hypotension develops, as an antidote. These complications make verapamil less desirable in treating patients with supraventricular tachycardia.

Diltiazem (recently available in intravenous form) now provides what appears to be a safer and more reliable treatment of this disorder than verapamil. Although a calcium channel blocker with a mechanism similar to verapamil, diltiazem exhibits considerably fewer cardiodepressant effects and is associated with fewer episodes of notable hypotension. In several small studies carried out in electrophysiology laboratories where tachycardia was induced electrically, diltiazem terminated 90% to 100% of the episodes with few episodes of serious hypotension.

This compares most favorably with verapamil, which has a similar reported conversion rate (greater than 80%) but a higher incidence of hypotension and cardiac depression.

Like verapamil, diltiazem is recommended for stable patients with narrow-complex supraventricular tachycardia as well as for the temporary control of rapid ventricular rate in atrial fibrillation or atrial flutter. The use of diltiazem, like that of verapamil, is contraindicated in patients with wide-complex tachycardia, sinoatrial or atrioventricular nodal disease, and recent β-blocker usage. The current recommended dose is 0.25 mg per kg given slowly by intravenous pyelogram over one to two minutes. If no response and no episodes of hypotension are seen after 30 minutes, the dose should be repeated at 0.35 mg per kg. Intravenous diltiazem is proving to be safe, effective, and well tolerated by patients with supraventricular tachycardia. It may soon supplant verapamil in the treatment of refractory tachycardia.

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Management of Combative Trauma Patients

THE EVALUATION IN AN EMERGENCY DEPARTMENT of an agitated, combative patient with major trauma can be difficult. It is important that physicians dealing with patients of this type have a systematic approach to their management. Combativeness by injured patients may be due to hypoxia, hypovolemia, head injury, drug or ethanol ingestion, pain, or psychogenic causes. Identifying and correcting the problem requires a physical examination and diagnostic testing. This may be impossible in a combative patient, however, leaving a clinician with three options: physically restrain the patient and delay diagnostic evaluation until the patient calms down, use a sedating agent, or invoke total chemical restraint with paralysis and intubation.

Physical restraint and observation is an inappropriate approach to a possibly injured patient. Attributing combativeness to intoxication or to psychogenic causes can be a fatal error in judgment.

Sedating agents used to control combative patients include narcotics, benzodiazepines, and butyrophenones. Narcotics and benzodiazepines have a rapid onset of action and are titratable and reversible. Respiratory depression and hypotension, however, are serious drawbacks with both classes of drugs. Butyrophenones (haloperidol and droperidol) have been suggested as the optimal sedating agents for the control of combative trauma patients. Both agents cause sedation with little effect on the respiratory drive. Possible complications of their use include prolonged sedation, hypotension, dystonic reactions, a neuroleptic malignant syndrome, and adverse interactions with ethanol or street drugs.

Total chemical restraint of a combative trauma patient with paralysis and ventilatory support has been called "inhumane" and "not justifiable." Some condemnation of this practice is based on the fear of iatrogenic complications, most important the possibility of paralyzing a patient and then being unable to ventilate that patient. Other possible complications of neuromuscular blockade include aspiration, hyperkalemia, and malignant hyperthermia. These complications, however, are rare; the risks must be weighed against the benefits of truly adequate airway control and expediting the diagnosis and management of serious injuries.

The management of combative trauma patients must be individualized. Hemodynamically stable combative patients with a low probability of major head injury can be managed with sedation alone using butyrophenones as the agents of choice. Combative patients with signs of a serious head injury should be managed from the start with rapid-sequence paralysis and intubation. Hemodynamically unstable patients should undergo rapid evaluation and resuscitation, and if it appears risky to sedate such patients without controlling their airway, neuromuscular blockade and sedation should be considered.

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Improving Emergency Department Response to Victims of Domestic Violence

MANY WOMEN who seek care in emergency departments are estimated to have symptoms directly or indirectly related to domestic violence. Some will present with injuries due to battering. Many others present with nontraumatic symptoms, such as depression, suicide attempts, chronic pain syndromes, hyperventilation, and sleep disorders. Some of the 15% to 25% of pregnant women who are battered will have pregnancy-related symptoms, such as pelvic pain, vaginal bleeding, or impending miscarriage.

Despite the prevalence of domestic violence, the diagnosis is frequently missed. Some reasons are cited in the literature for this failure to diagnose, including time constraints, failure of a patient to volunteer information, and the lack of training, prejudice, and misunderstanding on the part of medical personnel.

Although there may be clues that suggest domestic violence, from a patient's inappropriately flat or fearful demeanor, a central or defensive pattern of injuries, or the

abusive partner's overly solicitous or protective behavior, many cases of domestic violence will not be identified unless the victims are questioned directly about the existence of violence in their lives. Questions such as "Injuries like this are sometimes the result of violence in the home. Is this what happened to you?" or "Violence in the home is very common. Have you experienced verbal or physical assault in your home?" should be routinely incorporated into the history.

Victims of domestic violence have often been systematically cut off from friends and family. They may feel alone and that they have no one in whom to confide. They may think no one will believe their story. Frequently they feel that they are somehow to blame for what is happening to them. It is important for them to be told that they are not alone, that they do not deserve to be beaten, and that help is available. All emergency departments should have up-to-date lists of domestic violence agencies and other resources available in their communities. These measures and referrals are of therapeutic benefit.

Finally, since January 1992, the Joint Commission on the Accreditation of Healthcare Organizations has required that emergency departments have written policies and procedures for identifying, evaluating, treating, and referring battered adults. There is also a requirement for a plan to educate staff about domestic violence. Essential elements that should be incorporated into emergency departments' written domestic violence policies include a definition of domestic violence and its dynamics, a listing of common indicators suggesting domestic violence, details of appropriate documentation and evidence collection, specific interventions, referral information, and state reporting requirements.

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Conscious Sedation in the Emergency Department

ONE OF THE MOST IMPORTANT duties of an emergency department physician is to alleviate pain and anxiety. Failure to achieve this goal occurs for various reasons, not the least of which is the absence of an ideal agent. If such a drug or combination of drugs existed, it would be safe and effective, have a rapid onset and short duration of action, demonstrate minimal side effects, be easy and painless to administer, provide excellent analgesia and amnesia, and be reversible. Although the search for such an agent continues, the technique of conscious sedation using midazolam hydrochloride and either ketamine hydrochloride or fentanyl citrate comes close to satisfying many of these criteria.

The concept behind conscious sedation is to produce a state of analgesia and sedation with a minimally depressed level of consciousness. The patient should not require assistance with airway maintenance or protection and should be able to respond to physical and verbal stimuli. Indications for conscious sedation include, but are not limited to, rape examinations, the repair of tongue lacerations in children, fracture reduction, and to facilitate lumbar punctures, abscess drainage, and wound debridement. When using this technique, the patient should be monitored with a pulse oximeter and preferably should have had nothing by mouth for three hours. In addition, the physician must have experience with airway management and all the equipment necessary to do any airway intervention. Naloxone hydrochloride and flumazenil should also be available at the bedside.

Ketamine, a dissociative anesthetic and analgesic, has been in use for 20 years. It can be administered intramuscularly, intravenously, orally, or per rectum, produces excellent anesthesia, analgesia, and amnesia, and has rapid onset and recovery and a wide margin of safety. Unlike general anesthetics, ketamine supports the cardiovascular system and does not depress ventilation. Notable contraindications include increased intracranial pressure, use in neonates, respiratory infections, tracheal abnormalities, moderate hypertension, and congestive heart failure. For parenteral administration, the dosage is 2 mg per kg intravenously or 4 to 6 mg per kg intramuscularly. To administer orally, 8 to 10 mg per kg is the currently accepted dose. These regimens will typically produce dissociative anesthesia for 10 to 15 minutes, with the oral route sometimes producing effects lasting as long as 30 minutes. Midazolam (Versed) should be given to older children and adults to minimize the emergence phenomenon (mild hallucinations while awakening). It can be given intramuscularly or intravenously (0.05 mg per kg), orally (0.50 to 0.75 mg per kg), or nasally (0.3 mg per kg).

Another agent effective at producing conscious sedation is fentanyl. This drug is a short-acting narcotic with effects lasting less than an hour. It does not release histamine nor cause myocardial depression. The problem of chest wall rigidity is not seen with the low doses used in emergency departments. Mild respiratory depression can be substantially reversed with naloxone. The pulse oximeter is effective in detecting this event, however, and patients will usually respond to verbal instructions to breathe without requiring further intervention.

Fentanyl is typically given with midazolam to help with painful procedures. Like midazolam, fentanyl can be administered both parenterally and nonparenterally. The intramuscular and intravenous dosages are the same, 2 μg per kg. The nonparenteral route is through a transmucosal delivery system (lollipop). Its action begins in 15 to 30 minutes, with the optimal dose of 10 to 20 μg per kg. Mild facial pruritus is frequently reported with this delivery system, but it has no clinical consequences and does not interfere with drug administration. Patients usually recover enough to be discharged within two hours.

Other drugs, such as nitrous oxide, chloral hydrate,

and pentobarbital sodium (Nembutal), could also be included in this discussion, but they do not have as many of the desired traits as do ketamine, fentanyl, and midazolam. In addition, they are either too difficult to administer, last too long, or have no analgesic properties.

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Whole-Bowel Irrigation in the Management of Ingested Poisoning

WHOLE-BOWEL IRRIGATION is a recent and promising adjunct for gastric decontamination in some patients with toxic ingestions. Whereas the judicious use of gastric lavage and the liberal use of activated charcoal are generally adequate, there are special circumstances when whole-bowel irrigation is indicated.

Polyethylene glycol electrolyte solutions (GoLYTELY [Braintree Laboratories, Inc] and CoLyte [Reed & Carnrick]) were designed to be used for cleansing the gastrointestinal tract before an operation or colonoscopy. These solutions are isosmotic, and the salts are nonabsorbable, allowing them to be effective cathartics without causing fluid or electrolyte shifts.

For whole-bowel irrigation, the preparation is usually administered through a nasogastric tube at a rate of 2 liters per hour in adults (about 25 ml per kg per hour in children) and continued until the rectal effluent is clear, usually in four to six hours. This procedure is most readily performed in awake patients capable of sitting on a bedside commode, but it is also possible in obtunded patients. Whole-bowel irrigation is well tolerated in adults, children, and even in pregnant women. Contraindications to whole-bowel irrigation include ileus, perforation, and substantial gastrointestinal bleeding. The concomitant administration of activated charcoal and polyethylene glycol solutions decreases the binding capacity of the charcoal.

Whole-bowel irrigation is recommended for use in "body packers" (professional smugglers who ingest many carefully wrapped containers of drugs) and may be of some use in "body stuffers" (drug merchants who hastily swallow poorly packaged containers of drugs).

Patients who ingest potentially toxic iron and lithium carbonate preparations are good candidates for whole-bowel irrigation because these drugs are poorly absorbed by activated charcoal. A human model of lithium intoxication showed a 67% decrease in absorption with the use of only whole-bowel irrigation. A case series of pediatric iron ingestions showed, by serial x-ray films, the inadequacy of gastric lavage alone and the subsequent efficacy of whole-bowel irrigation in removing intact pills.

Whole-bowel irrigation may have a role in the treatment of patients who ingest sustained-release preparations of various medications. Logically, the most rapid method of removing sustained-release tablets from the body would minimize their toxic effects. Studies of the procedure in this subgroup have yielded conflicting results, however. A human model of a nontoxic sustained-release salicylate ingestion showed whole-bowel irrigation to be superior to activated charcoal. An awake dog model of a toxic dose of sustained-release theophylline showed no decrease in absorption with whole-bowel irrigation compared with activated charcoal. No clinical trials have been done assessing the efficacy of whole-bowel irrigation in any clinical scenario.

The use of whole-bowel irrigation in serious intoxications of iron, lithium, and sustained-release drugs may be considered as an adjunct in these difficult cases.

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Diagnosing Acute Cardiac Ischemia

ESTIMATES OF THE INCIDENCE of missed diagnoses of acute myocardial infarction in emergency departments range from 2% to 5%. Compared with physician judgment, computerized statistical predictive models show a trend toward higher specificity (that is, fewer patients are admitted to rule out myocardial infarction), but their sensitivity in detecting myocardial infarction is not improved (no fewer missed myocardial infarctions). An artificial neural network may prove to be a sensitive and specific mathematical model for predicting the presence of myocardial infarction.

Electrocardiography (ECG) is the most widely used diagnostic study in the evaluation of chest pain in emergency departments. As many as a quarter of all missed myocardial infarctions are attributable to a misinterpretation of the initial 12-lead ECG, however. Unfortunately, the initial ECG reveals ST-segment elevation in only about half of all patients with acute infarctions. The sensitivity of the ECG for acute cardiac ischemia may be enhanced by the use of serial ECGs, right-sided chest leads (15 leads), and even back leads (22 leads), as well as continuous computerized ECG-trend monitoring to detect beat-to-beat changes in QRS complex structure and ST-segment shifts.

Newer immunochemical assays have been developed that can detect early, small increases in the creatine kinase isoenzyme, CK-MB. Creatine kinase isoenzyme measurements over the first three to four hours after a patient

comes to an emergency department can improve the accuracy of diagnosing infarction in patients with nondiagnostic ECGs. The number of hours of chest pain is key to interpreting cardiac enzyme results. Myocardial infarction patients with chest pain for 3, 6, 9, and 12 hours had elevated CK-MB values in nearly half, more than half, greater than 75%, and 100% of cases, respectively. About 80% of all patients with myocardial infarction with nondiagnostic ECGs had elevated CK-MB levels within three hours of presentation; the combined sensitivity of serial ECGs and CK-MB determinations in emergency departments approaches 90%.

Myoglobin is released earlier than CK-MB from damaged myocardial cells (within 2 to 4 hours), but it disappears from the serum within 6 to 12 hours, about the time of the expected CK-MB elevation. Serial measurements using new rapid assays for myoglobin may be 100% sensitive for detecting myocardial infarction in the first six hours after the onset of chest pain. Other serum markers of myocardial damage, such as creatine kinase-MM subtypes, light-chain myosin fragments, and the troponin in protein, are currently under investigation. Troponin appears to have early diagnostic characteristics similar to those of CK-MB in patients with infarction. It also detects about half of the patients with unstable angina, and levels remain elevated for days after the infarction.

A trend in the evaluation of chest pain is the introduction of cardiac emergency or chest pain centers, usually within the confines of existing emergency departments. The diagnostic tools described above are combined with traditionally nonemergency cardiac testing. Echocardiography can reveal regional wall motion abnormalities within the first hour after coronary artery occlusion occurs. Thallium and technetium scintigraphy can show areas of decreased myocardial perfusion within four to six hours of infarction, but share the same problem as echocardiography in distinguishing new from old infarcts. A preliminary study of treadmill exercise stress testing in 32 emergency department patients with atypical chest pain suggests that coronary artery disease can be ruled out in carefully selected patients. With demands for more rapid and accurate diagnosis and for better resource use, the future evaluation of chest pain patients will most likely involve some type of outpatient holding area in emergency departments.

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Prehospital 'Do-Not-Resuscitate' Orders—A New Option

One of the most difficult ethical issues in medicine is when and under what circumstances to withhold what are collectively referred to as "resuscitative measures." Practicing physicians are familiar with do-not-resuscitate (DNR) orders in the hospital setting; DNR orders spare patients undesired and often futile interventions. Yet physicians also need to know about prehospital DNR systems and to take action to make sure all required documentation is in place before a critical event. Health care professionals have a responsibility to educate their patients about the appropriate use of the prehospital system. This includes not only when to call 911, but when not to call.

Despite educational efforts, families still call 911 for terminally ill patients. Families desire treatment short of resuscitation; others seek verification that death has occurred; still others think they are expected to notify authorities through an emergency number. Prehospital personnel may have only seconds in a confused situation to determine a patient's resuscitation status.

In light of the natural tendency to call the emergency 911 number when a death occurs, physicians must plan ahead to ensure that appropriate patients possess valid prehospital DNR orders. A well-designed prehospital DNR system avoids subjecting patients to unwanted and invasive measures, takes pressure off families in crisis situations, and relieves professionals of uncertainty surrounding legal obligations to initiate unwanted resuscitative measures.

New California state guidelines strongly encourage local agencies to enact prehospital DNR protocols. Once signed by a physician and the patient, prehospital DNR orders indicate that the patient or surrogate understands the advantages and disadvantages of attempted resuscitation, is making an informed decision, and wishes to proceed with a DNR order. Patients are offered medallions inscribed with "Do Not Resuscitate—EMS" similar to the Medic Alert bracelet. The new statewide DNR form will be respected by prehospital personnel no matter where the patient is.

Emergency medical system protocols regarding prehospital DNR status commonly include provisions of palliative treatment despite the DNR status; guidelines for the management of the deceased, including removal of the body; and access to grief-support counseling for families, as well as "critical-incident stress debriefing" for providers, as needed. In this way, costly resuscitation attempts will not be started if they are not desired or medically indicated. By signing prehospital DNR orders, physicians will spare their patients intrusive, unwanted, and futile interventions and allow prehospital health care providers to honor a patient's right to death with dignity.

The California Medical Association (CMA) Committee on Emerging Trends and the California State Emergency Medical Services Authority have produced a standard DNR request form now available to physicians

through the CMA (415-541-0900, extension 5175); several other states are developing or have developed similar systems.

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Alerts, Notices, and Case Reports

Bilateral Bell's Palsy and Aseptic Meningitis in a Patient With Acute Human Immunodeficiency Virus Seroconversion

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SINCE FIRST REPORTED in 1985,[1] the acute retroviral syndrome has been increasingly recognized in patients infected with the human immunodeficiency virus (HIV). Cases typically present with fever, myalgia, headache, rash, and lymphadenopathy and can easily be mistaken for mononucleosis or influenza. Occasionally neurologic complications—including aseptic meningitis, encephalopathy, neuropathy, myelopathy, and brachial neuritis—develop in association with primary infection. Except for the encephalopathy, which occurs simultaneously during the acute phase, the other manifestations tend to be seen about three weeks after the onset of the primary illness.[2] Bell's palsy has been reported during these episodes and has also been seen in patients already known to be HIV-seropositive.[3,4] Wechsler and Ho in 1989 first reported the case of a patient with bilateral Bell's palsy at the time of seroconversion.[5] Cerebrospinal fluid findings were not reported because no lumbar puncture was done. We report the case of a similar syndrome in a patient with acute seroconversion and the additional finding of aseptic meningitis.

Report of a Case

The patient, a 32-year-old male homosexual intravenous drug injector, was seen because of bilateral facial weakness. Four weeks before being seen he had been admitted to hospital because for three days he had had abdominal pain, fever, sweats, chills, and lethargy but no headache. An examination showed a temperature of 39.1°C, mild abdominal tenderness, and diffuse lymphadenopathy. No rash was noted. He had no nuchal rigidity or other neurologic abnormalities. His leukocyte count was 3.3×10^9 per liter (3,300 per μl) with 0.47 polymorphonuclear leukocytes, 0.34 bands, and 0.12 lymphocytes. An absolute $CD4^+$ count was 390 cells $\times 10^6$ per liter, the $CD4^+$:$CD8^+$ ratio was 1.4, and an enzyme-linked immunosorbent assay (ELISA) test for HIV was negative. Over the next few days, all of his symptoms resolved, and he was discharged home without a definitive diagnosis.

One week before we saw him, he noted the painless onset of right-sided facial weakness. Three days later he noted that the weakness now involved the left side of his face. He otherwise felt well and had no other complaints, but on questioning said that he did have a mild nonlocalized headache. He lived in Sacramento, California, and had no recent travel history. He was admitted to the neurology service for evaluation.

On examination, he was afebrile, appeared comfortable, with the only abnormality being bilateral peripheral facial musculature weakness, right greater than left, with decreased taste discrimination on the right anterior two thirds of the tongue. Detailed neurologic, ophthalmologic, and mental state examinations elicited no other abnormalities. There was no nuchal rigidity. Laboratory studies included unremarkable values on a liver panel, an erythrocyte sedimentation rate of 9 mm per hour, and a leukocyte count of 8.6×10^9 per liter with 0.38 polymorphonuclear leukocytes, 0.18 bands, and 0.31 lymphocytes. A chest x-ray film was normal, and heterophile and VDRL tests and blood cultures were negative. Head computed tomographic scan and magnetic resonance imaging with gadolinium were normal. Lumbar puncture revealed a cerebrospinal fluid (CSF) glucose level of 3.1 mmol per liter (55 mg per dl; a blood glucose level was 4.3 mmol per liter [78 mg per dl]), protein 1.66 grams per liter (166 mg per dl), leukocyte count 78×10^6 per liter (0.99 lymphocytes), and no erythrocytes. No organisms were seen on Gram's stain, and cultures were negative for bacterial, fungal, viral, and mycobacterial organisms. The CSF specimen was tested for *Coccidioides immitis* antibodies, *Toxoplasma gondii* antibodies, *Cryptococcus neoformans* antigen, and VDRL, all of which were negative. Serum antibody tests were negative for *Borrelia burgdorferi*, herpes simplex virus, and varicella zoster virus. A Tensilon test was negative. Electromyography and nerve conduction studies were interpreted as consistent with primarily peripheral facial nerve lesions, right greater than left, without evidence of demyelination or abnormality of the neuromuscular junction. The $CD4^+$ count was now 718 cells $\times 10^6$ per liter, with a $CD4^+$:$CD8^+$ ratio of 0.3. A repeat ELISA and Western blot assays were both positive for HIV type 1.

During a period of observation in the hospital, without antiretroviral or other therapies, he had spontaneous lessening of his facial palsy and resolution of his headache. A repeat lumbar puncture a week after the first one continued to show lymphocytic pleocytosis. By four weeks after his symptoms began, the palsy had nearly completely resolved, and he continued to feel well.

Discussion

This patient's transient facial diplegia probably di-

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ABBREVIATIONS USED IN TEXT

CSF = cerebrospinal fluid
ELISA = enzyme-linked immunosorbent assay
HIV = human immunodeficiency virus

rectly resulted from his acute HIV seroconversion and was not a consequence of any other infectious or malignant process. His initial hospital admission was almost certainly due to acute HIV infection with its characteristic transient decline in CD4+ cell count followed by the development of seropositivity and a rebound in T-helper cells. In addition, he had evidence of an ongoing aseptic meningitis, which may have been the cause of the palsy. Cerebrospinal fluid abnormalities were reported in all seven previously known HIV-positive patients evaluated for unilateral Bell's palsy[4] and are a common finding in HIV-infected patients without focal neurologic abnormalities.[6,7] It has been postulated in cases like this that the delayed occurrence of neurologic abnormalities until after the acute primary illness has resolved may reflect an exaggerated host response to the infection rather than a direct result of the virus itself.[2] In contrast to the progressive HIV-related neurologic abnormalities that can develop later in the disease course, these acute complications are much more likely to resolve spontaneously in a few weeks, as seen in this patient.[8,9]

The nearly normal CD4+ count during this patient's second hospital admission is also a good example of the possible lack of correlation between the degree of immune dysfunction and the onset of acute HIV neurologic disease. In a series from Africa, Belec and colleagues observed that "facial palsy can affect healthy, symptom-free HIV carriers with only a slight decrease in immunological indices."[3(p1421)] It has been hypothesized that neurotropic HIV strains differ biologically from those linked to rapid immune dysfunction.[8] Therefore, in a patient at risk, despite a normal CD4+ count or lack of other systemic symptoms, HIV infection should be considered as the possible cause of newly occurring facial palsy. If initial screening serologic tests are negative, consideration should be given to repeating them later, ordering a Western blot test, or doing one of the new, more sensitive assays such as the polymerase chain reaction.[10]

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Recurrent Angioedema and Urticaria

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ANGIOEDEMA is a potentially life-threatening condition in which a well-demarcated localized edema involves the deeper layers of mucous membranes and the skin, including the subcutaneous tissue. During an acute episode, patients may have edema of all or part of an extremity, the face, tongue, epiglottis, larynx, respiratory tract, and gastrointestinal tract. Involvement of the respiratory tract can cause dyspnea, dysphasia, stridor, wheezing, and respiratory arrest.

We describe the case of a patient with recurrent angioedema of the face, neck, and pharynx severe enough to require tracheal intubation and an urticarial skin rash of the distal upper and lower extremities. This case illustrates the possible severity of angioedema and the need to investigate thoroughly cases of recurrent angioedema for causative factors.

Report of a Case

The patient, a 60-year-old woman, had hypertension that had been treated with enalapril maleate, an angiotensin-converting enzyme (ACE) inhibitor, for 20 months before admission; chronic polyarthritis treated with piroxicam; and macrocytic anemia associated with chronic alcohol abuse. Since starting the enalapril therapy, the patient was evaluated on six different occasions in a military medical center for recurrent angioedema of the face and urticaria on the upper and lower extremities. Each time her symptoms were relieved with epinephrine, antihistamines, and corticosteroids. The patient did not have sensitivity to sunlight, cold, or heat and had no apparent renal, hepatic, intestinal, or central nervous system dysfunction. Her family history was negative for an-

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ABBREVIATIONS USED IN TEXT

ACE = angiotensin-converting enzyme
D_LCO = diffusing capacity of the lungs for carbon monoxide
Ig = immunoglobulin
SLE = systemic lupus erythematosus

gioedema, allergies, urticaria, systemic lupus erythematosus (SLE), and other autoimmune disorders.

On the day of admission, the patient again had angioedema of the face, tongue, epiglottis, and larynx and was seen at the military clinic in severe respiratory distress. She was nasally intubated, treated with epinephrine, and transported to the University of Nevada Medical Center, Las Vegas. On admission, the patient was agitated and had obvious swelling of her face, lips, tongue, eyelids, and throat. Urticarial and purpuric rashes were noted over the forearms. She was afebrile with a heart rate of 112 beats per minute, a blood pressure of 149/96 mm of mercury, and a respiratory rate of 22 inspirations per minute. She was given diazepam for agitation in addition to epinephrine, antihistamines, and corticosteroids. All previous medications were discontinued on admission. For the next 24 hours she responded well with supportive care and was consequently extubated and transferred to a medicine floor with a diagnosis of angioedema due to ACE inhibitors.

In the hospital, the following laboratory data were obtained. Initially the patient's leukocyte count was 11.2×10^9 per liter (11,200 cells per μl), the erythrocyte count was 3.33×10^9 per liter, hemoglobin 119 grams per liter (11.9 grams per dl), hematocrit 0.36 (36%), platelets 216×10^9 per liter (216,000 per μl), and a mean erythrocyte corpuscular volume of 107.5 fl (107.5 cu μm), consistent with a macrocytic anemia. Erythrocyte folate and vitamin B_{12} levels were, however, within normal limits. Complement studies showed a decrease in CH_{50} (total complement). Serum studies showed no detectable antinuclear, antimitochondrial, or antismooth muscle antibodies, rheumatoid factors, cryoglobulins, or cold agglutinins.

A skin biopsy specimen of the purpuric rash showed a perivascular infiltrate of chronic inflammatory cells. A subsequent biopsy of an urticarial lesion, however, revealed leukocytoclastic vasculitis in the dermis: perivascular infiltrates of polymorphonuclear leukocytes with occasional eosinophils, extravasated erythrocytes, and nuclear dust. Immunofluorescence showed immunoglobulin (Ig)G, IgA, and C3 in the dermal papillae, IgA in the basement membrane, and IgM in superficial blood vessels. A bone marrow biopsy showed slightly megaloblastoid erythroid maturation, but no evidence of lymphoproliferative or myeloproliferative malignancy.

The patient recovered completely and was discharged four days after admission. Complement studies of blood obtained during her hospital stay and after discharge revealed markedly decreased C1q protein level and C1q function but normal C1r and C1s levels, decreased to normal C2 protein level and decreased C2 function, a decreased C4 level, low to low-normal C3 level, and normal levels of both C1-inhibitor protein and function (Figure 1). These results indicate activation of the classical complement pathway. Immunoglobulin G autoantibody to C1q was detected in the patient's serum in moderately high titer (42 standard deviation units [normal ≤ 2]). The patient's disease was diagnosed as hypocomplementemic urticarial vasculitis syndrome, a presumed autoimmune disorder characterized by urticarial vasculitis, angioedema, arthritis or arthralgia, profoundly decreased serum C1q levels, and the presence of serum anti-C1q autoantibody.[1-5]

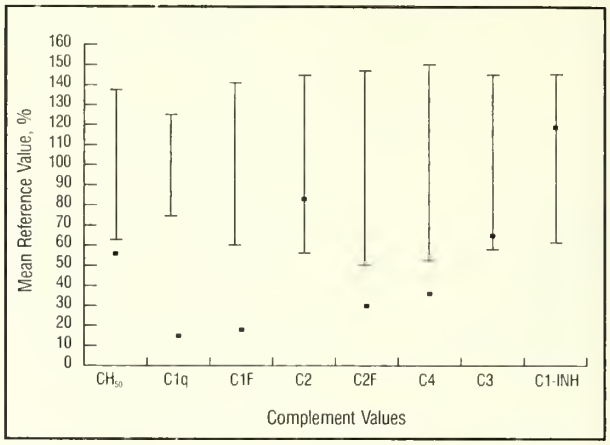

Figure 1.—The patient's complement values (■) are expressed as a percentage of the mean reference value (100%). The normal range is represented as 2 standard deviations from the mean. Represented are total complement (CH_{50}), C1q, C2, C4, C3, and C1-inhibitor (C1-INH) levels, and the complement function of C1 (C1F) and C2 (C2F).

Because this syndrome is associated with obstructive airway disease (J. J. Wisnieski, A. Bear, J. Christensen, et al: "Hypocomplementemic Urticarial Vasculitis Syndrome [HUVS]: A Review of 27 Patients With a High Incidence of Pulmonary and Renal Involvement," unpublished data, February 1992),[6] pulmonary function tests were done two weeks after discharge when her respiratory symptoms had completely resolved. Spirometric results were suggestive of a mild small airway obstruction with no change in her forced vital capacity or forced expiratory volume and a 40% improvement in her forced expiratory flow at midexpiratory phase after bronchodilator treatment. Lung volumes were normal, but the diffusing capacity of the lungs for carbon monoxide (D_LCO) and the ratio of the D_LCO to the alveolar ventilation were severely reduced. These results were consistent with an increase in airway resistance.

Discussion

Episodic angioedema is a condition often seen in clinical practice, and its differential diagnosis is extensive (Table 1).[7-9] The hereditary form of angioedema is an uncommon autosomal dominant disease in which the C1-inhibitor function is diminished because of decreased synthesis of normal C1-inhibitor (85% of cases of hereditary angioedema; type I) or synthesis of a dysfunctional C1-inhibitor molecule (15% of cases; type II).[8,9] The

TABLE 1.—*Classification of Angioedema**

Hereditary Angioedema
C1-inhibitor deficiency
Type I ..... Decreased synthesis of C1 inhibitor
Type II ..... Functionally defective C1 inhibitor
Acquired Angioedema
C1-inhibitor deficiency
Type I (AAE I) .... Associated with B-cell lymphoproliferative disease
Type II (AE II) .... Autoimmune, no underlying disease
Immune complex induced
Serum sickness, hypocomplementemic urticarial vasculitis syndrome, systemic lupus erythematosus (rare)
Drug induced
ACE inhibitors, aspirin, NSAIDs
Allergic (IgE-mediated)
Foods allergens
Inhalants allergens
Bites and stings
Parasitic infections
Drugs and chemical reactions
Direct histamine releasers
Morphine, codeine, iodinated radiocontrast media
Associated with underlying disease
Urticaria pigmentosa
Cutaneous or systemic mastocytosis
Physical stimuli
Cold, heat, sunlight, pressure, water, vibration
Idiopathic angioedema

ACE = angiotensin-converting enzyme, NSAIDs = nonsteroidal anti-inflammatory drugs

*Adapted from Gelfand et al,[7] Megerian et al,[8] and Sim and Grant.[9]

pathogenesis of the disorder is not fully understood, but it is clear that decreased C1-inhibitor function permits activated C1s to cleave C4 and C2. Recent work suggests that peptides generated by plasmin-mediated cleavage of C2b, a primary cleavage fragment of C2, are pathogenic factors in patients with hereditary angioedema.[10] The simultaneous occurrence of angioedema and urticaria virtually eliminates hereditary angioedema from diagnostic consideration.

Agents, factors, or diseases associated with nonhereditary angioedema include drugs; acquired C1-inhibitor deficiency[7,8,11]; immunologic disorders like serum sickness, hypocomplementemic urticarial vasculitis syndrome, and rarely SLE[4,5,7]; and allergies, physical stimuli, and idiopathic causes.[7,8,11]

Drug-induced angioedema is a form of nonhereditary angioedema and can be associated with the use of ACE inhibitors. In this instance, the mechanism of disease is mediated by an increase in bradykinin levels and a diminution of angiotensin II levels due to ACE-inhibitor treatment. It is not an allergic reaction nor complement mediated, and it is not associated with urticarial skin lesions.[12,13]

The acquired deficiency of C1 inhibitor is relatively rare. In a 1989 review, only 40 cases had been reported.[5] Of these, two types of disease could be identified. One occurred in 34 patients with B-cell lineage lymphoproliferative disorders (acquired angioedema type I), and the other in the remaining patients could be characterized by the presence of autoantibodies directed toward the C1-inhibitor enzyme (acquired angioedema type II).[11,14,15]

Recently it has been suggested that in patients with acquired angioedema type II, a structural and functionally normal 105-kilodalton C1 inhibitor is synthesized and secreted. Subsequently, it is complexed by an autoantibody, and following an enzymatic interaction, the C1 inhibitor is altered to produce a dysfunctional 96-kd protein.[16,17]

Hypocomplementemic urticarial vasculitis is a rare syndrome of recurrent urticarial vasculitis, arthralgia or arthritis, low serum C1q, C4, and often C3 levels, and IgG anti-C1q autoantibody in 95% to 100% of patients. As many as 70% of patients with this syndrome also have angioedema or eye inflammation (Wisnieski and associates, unpublished data). Its cause is unknown, but it is likely an autoimmune disorder related to SLE.[18] It is separable from SLE on the basis of severe obstructive airways disease, angioedema, and eye inflammation, which occur commonly in patients with hypocomplementemic urticarial vasculitis syndrome but rarely in those with SLE. An additional finding that may be characteristic of the syndrome is discordance between levels of C1q (profound decrease) and those of C1r and C1s (normal).[4] The pathogenesis of urticaria and angioedema in this disorder is likely to involve C3a and C5a, the smaller of the activation fragments of C3 and C5, and perhaps C2 peptides as well, generated by C1s and pepsin, as in hereditary angioedema. Angioedema in this syndrome is usually not life-threatening, but Zeiss and co-workers reported the cases of two patients who also required intubation.[4] Angioedema typically accompanies or follows the development of urticarial lesions in this disorder, but angioedema preceded urticaria in our patient by at least 24 months. To our knowledge, the presentation of the syndrome in this patient is unique.

The analysis of serum complement components will determine if angioedema is caused by C1-inhibitor deficiency.[9] If normal levels of C4 and C2 are found in a patient's serum during an episode of angioedema, C1-inhibitor deficiency is not the cause. In contrast, normal serum levels of C4 and C2 between episodes do not eliminate C1-inhibitor deficiency as the cause. The measurement of serum C1-inhibitor protein will detect most patients with this deficiency, whether hereditary or acquired. In the remainder, the serum C1-inhibitor protein level is normal, but C1-inhibitor function in serum is not. Most of these patients have hereditary angioedema type II, and the minority have acquired angioedema type II as described earlier. The measurement of C1 or C1q will determine if C1-inhibitor deficiency is hereditary or acquired: C1 and C1q levels are greater than 50% of normal in hereditary angioedema I and II but less than 50% in acquired angioedema I and II (Table 2).[7,9,16,17]

In a patient with angioedema, decreased C4, C2, and C3 levels but normal C1-inhibitor function indicates activation of the classical complement pathway and suggests vasculitic involvement of the deeper dermal vessels. The measurement of C1q confirms the classical pathway activation. The development of angioedema as a manifesta-

TABLE 2.—*Complement Abnormalities in Angioedema**

Type of Angioedema	Complement Abnormality					
	C1-INH Function	C1-INH Level	C1 Level	C2 Level	C3 Level	C4 Level
Hereditary type I	↓↓	↓↓	N	↓	N	↓↓
Hereditary type II	↓↓	N	N	↓	N	↓↓
Acquired C1-INH deficiency	↓	↓	↓↓	↓↓	N	↓↓
Others	N or ↑	N or ↑	N or ↓	N or ↓	N or ↓ or ↑	N or ↓

C1-INH = C1-inhibitor, N = normal, ↓ = decreased, ↑ = increased

*Adapted from Gelfand et al[7] and Sim and Grant.[9]

tion of vasculitis without findings in the upper dermis (urticaria, purpura) is apparently rare in immune-mediated disease like SLE, serum sickness, and cryoglobulinemia. In a patient with angioedema, normal complement studies virtually eliminate a humoral immunologic cause of angioedema.

In the acute setting, angioedema can be life-threatening and must be aggressively treated with epinephrine, antihistamines, and corticosteroids. If the patient fails to respond, supportive measures such as intubation or tracheostomy may be necessary. Fresh frozen plasma can be administered in life-threatening attacks.[9] For persons known to have hereditary angioedema, purified C1-inhibitor infusion has been used with success.[19,20]

Most forms of angioedema do not require long-term maintenance therapy. The long-term treatment of acquired angioedema requires identification of the underlying cause and its elimination whenever possible. The management of hypocomplementemic urticarial vasculitis syndrome is empiric. Initially, a patient with urticaria (with or without angioedema) and low complement levels should have a biopsy of skin lesions to confirm vasculitis and serologic testing for anti-C1q autoantibody. Before treatment, a patient with this syndrome should be evaluated for ocular, pulmonary, and renal involvement. Urticarial vasculitis responds poorly to histamine H_1 and H_2 blockers, indomethacin, and colchicine. A regimen of prednisone, 30 to 60 mg a day for as long as three months, usually suppresses joint, skin, and eye manifestations, but these often recur as the prednisone dose is tapered. Dapsone, hydroxychloroquine sulfate, and azathioprine appear to be effective in suppressing urticarial lesions (Wisnieski and associates, unpublished data, February 1992).

With patients taking ACE inhibitors for hypertensive disease, the substitution of another antihypertensive such as a calcium channel blocker or β-blocker is indicated. In some cases, treatment of the underlying cause might not be possible (such as for acquired C1-inhibitor deficiency), and these patients have benefited from the administration of attenuated androgens and antifibrinolytic agents such as aminocaproic acid and tranexamic acid.[8,9,11,21]

Summary

The case reported here illustrates the life-threatening aspects of angioedema and the need to thoroughly investigate the possible causes of this clinical finding. As discussed, the causes of angioedema are numerous. Commonly implicated in drug-induced angioedema are antihypertensive ACE inhibitor drugs, as was originally thought with this patient. Because of her skin lesions and macrocytic anemia, further studies were done. These studies led to a diagnosis of hypocomplementemic urticarial vasculitis syndrome, an uncommon to rare form of acquired angioedema, urticarial vasculitis, arthritis, and obstructive airway disease associated with the production of autoantibodies to C1q. It is an autoimmune disorder related to but separate from SLE.

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Commentary

Cross-cultural Communication in the Physician's Office

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Physicians are increasingly called on to provide care for patients whose cultures differ from their own. I describe strategies, attitudes, and investigative methods that will enhance the experience of cross-cultural medicine for both patients and physicians.

(Mull JD: Cross-cultural communication in the physician's office. West J Med 1993; 159:609-613)

Society in the western United States is increasingly multicultural and multiethnic. Virtually all of us who practice or teach medicine here regularly see patients whose language we do not speak and whose medical beliefs, practices, and expectations differ from our own. While this has always been so for physicians affiliated with university hospital teaching programs, the need for cross-cultural care has now penetrated every corner of the medical community. Even health maintenance organizations serving affluent coastal areas frequently need interpreters and culture brokers. In greater Los Angeles, for example, patients may speak any of 103 different languages.

Busy practitioners have limited time to research the literature or to consult with professional anthropologists. Drawing on my own clinical experience over the years, I outline basic issues in cross-cultural health care and present case histories that illustrate the importance of those issues.

Caring for Patients—It Works Best for Those Who Seem to Care

Patients have an uncanny ability to tell who is really interested in helping them—who really cares about them as people. They can tell by the concern shown in physicians' eyes when they listen, and they can tell by the respect accorded them by office staff. Whereas most of us know this to be true of patients from our own culture and language group, it is no less true for people whose language we do not speak. Even when physicians may be working through interpreters, patients can tell if they are really interested, and taking the time to let one's genuine interest and feelings show pays off.

When physicians are friendly and helpful, patients are more likely to reveal their concerns, which enhances a physician's ability to build rapport and to develop a repertoire of knowledge—both of which are essential for improving the quality of medical care. Learning about a given cultural group's major holidays, the general principles of their traditional medicine, and a few key phrases from their language that can be used in greetings and during examinations goes far to prevent any aura of alienation that might otherwise block cross-cultural communication.

What People Do Before They Come to the Doctor

Everyone does something before seeing their physician. Self-medication is practiced in more than 90% of illnesses.[1] In the process, advice is almost always sought from someone else about the nature of the problem and what to do about it.[2] That someone may be a neighbor, an influential member of an ill person's extended family, or even a community leader—as in the case of the Lao Hmong, who tend to go to their leaders for advice just as they did in the old country. In fact, there have been boycotts of hospitals by the entire Lao Hmong community when this tradition was not respected and emergency surgical procedures were done without the usual process of consultation and consent.

Often home remedies or other traditional treatments are advised by both lay health consultants and traditional or alternative healers. Such healers are consulted much more frequently than physicians may realize.[3] Physicians should always ask patients what they have done before coming in, both to learn about possible sources of delay in treatment and to understand parallel systems of medical care that may be used concurrently with biomedicine. Although alternative systems are sometimes harmless and

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comforting havens of culturally familiar support, they can also be siren songs luring patients away from more effective therapy.

Finding Out What Patients Think and Do

Learning about people's beliefs and behaviors is the core of applied medical anthropology, and it is centrally important for physicians practicing across cultural boundaries. Clinicians should routinely ask patients what they think is the cause of their illness. The trick is how and when to ask.

One of my medical students whose field project took her to a barrio clinic reported back to me that she was learning nothing. People responded to her queries by asking, "How should I know why I'm sick? I've come to the doctor because *he's* the expert!" It turned out, however, that the student was jumping right into the subject a few moments after meeting the patients. I advised her to first establish a relationship by talking with them about their lives and families. She returned to the same clinic using this new approach, and the patients' stories began to flow.

Suddenly the folk beliefs of Mexico were being revealed. My student learned, for example, that many pregnant women wore a bright new safety pin on their underwear to deflect dangerous rays from an eclipse, which could cause a child to be born with a cleft lip. Some women confided that eclipses could occur suddenly, without notice, and without scientists knowing about them. They also said that fright sickness *(susto)* could cause a fallen fontanel, even in adults, and that it could usually be diagnosed only by a traditional healer. Such a healer would know how to treat it by putting her index finger in the victim's mouth and pushing up on the palate so that the fontanel could pop back in place.

Family as a Source of Insight and Locus of Persuasion

Even a physician who is familiar with a particular cultural group will think from time to time that patients are doing something that does not make sense. In such cases, meeting with the family along with the patient often provides important insights.

In an instance of "therapeutic failure" involving an Italian-born woman, I learned that the patient was convinced that she had been hexed by someone's evil eye. She believed that until the hex was removed, she was never going to be entirely well. This emerged from a discussion with the family about her "total body pain"—which never seemed to get better with anything that I did.

By meeting with families of Vietnamese patients whose blood pressure levels would not come down, I learned that Vietnamese people commonly believe that Western medicines are too strong for them because they are smaller than we are. Thus, they often take only half of whatever dose of medicine physicians recommend. I now take pains to explain to such patients that the proper adjustments for their size and weight have already been made and that the medicine will not work unless they use the proper "Vietnamese" dose of medication that I am prescribing.

Families are often more cohesive and powerful in other cultures than they are in our own. Physicians who recognize this can use the family both to better understand a patient's behavior and complaints and to bring group influence to bear on the patient. Conversely, a physician who goes against the advice of a grandmother or a mother-in-law in such a cultural group may have virtually no chance of prevailing. Often, for example, older women are the critical persons who must be convinced about the need to treat a young bride or a young pregnant wife. Even in the context of a busy American medical office practice, such shadowy figures—who frequently do not speak English and seem "old-fashioned"—can wield massive influence. They should be sought out and included in decision making so they are part of the solution, not part of the problem.

Physicians must understand that in many societies, patients do not make decisions on their own. Elders in the family decide whether or not someone is sick, what are the likely causes, and who, if anyone, is the appropriate person to visit for therapy. But a strong sense of family can also be used to persuade patients to seek out and follow medical advice. One must sometimes go first to the young women to help the old. The tradition of self-sacrifice is so strong among older Mexican-born women, for instance, that they may not go to their physicians for Pap smears, even with alarming symptoms such as postmenopausal vaginal bleeding, unless their adult daughters plead with them to look after their health for the sake of their families. The same type of reasoning succeeded with Hispanic men in northern California in a campaign against high blood pressure and heart disease. During the Stanford Heart Disease Study, television spots appealed to men as heads of families to get their blood pressure checked and to stop smoking for the sake of their families who loved and depended on them (C. Gibson, oral communication, September 1984).

Going Beyond the History and Physical Examination

The conventional history and physical examination does not facilitate learning about patients' family lives or their traditional health beliefs and practices. Instead, it is like an algorithm designed to lead physicians to the single Oslerian diagnosis that explains all the symptoms. It will not work when the cause is something outside the realm of physical disease or when the patient presents with a set of symptoms that are "impossible" according to the biomedical model of illness.

For example, patients from other cultures frequently describe feelings and sensations that seem to make no scientific sense, such as Vietnamese patients who complain of feeling "tired" deep in the chest. Translated into Western models, this complaint corresponds best to depression, hopelessness, mental exhaustion, or exasperation. But it *must* be translated; it should not simply be written off. Similarly, Hispanic patients often say that they "hurt

all over," and I have found that this, too, is commonly associated with depression.

Other Themes in Cross-cultural Medicine

There is now an abundant literature on beliefs and practices of many groups that have come to the United States from other parts of the world.[4-10] Although some patients may not adhere to these specific beliefs and behaviors because of their education or their length of stay in the United States, physicians should be familiar with concepts that are frequently encountered because they represent general attitudes that have clinical importance.

Fear of Blood Loss

People from many developing countries fear that blood that is drawn for laboratory tests will not be replaced and that the blood loss will weaken the body. Some may even withdraw from treatment to avoid the procedure. This problem should be anticipated and the procedure approached as a negotiation. For example, the physician could ask, "How would you feel about having some blood taken?" If abject panic comes over a patient's face, the test should be deferred until the blood replacement process can be explained to the patient.

Fear of Cold

A fear of cold, especially for women in the first 40 days after giving birth and for newborn children, is so strong in many cultures that even a severe illness will not be enough to prompt people to go outside to seek help from a physician during the winter months. Thus, it is important for physicians to explain that with proper bundling up with blankets, new mothers and their infants can safely come to health facilities.

Traditions of Male Dominance

Another useful generalization is that in most developing countries, men have an important role in the family as leaders and decision makers. Physicians must involve them—especially husbands—in discussions of the medical problems of family members. This should be the case even if the men intentionally absent themselves from the physician's office, an environment in which they may sense a loss of power. My experience has been that husbands and fathers very much appreciate it when I show respect by discussing the diagnosis and treatment with them.

Conservatism in Sexual Matters

In many cultures, paternal protectionism reaches its zenith in the protection of teenaged girls. This does not mean that the girls do not quickly become Americanized, but their parents are much less likely to embrace American sexual liberty, and one has to negotiate delicately about such matters as pelvic examinations or birth control. At times I have resorted to distracting the parents while a woman staff member talked with the girl about birth control or venereal disease problems or made arrangements for her to return alone for a pelvic examination. Although this is a disquieting way for a physician to relate to families, it is necessary at times when girls cannot let their foreign-born parents know that they are sexually active.

Lack of a Preventive Health Orientation

The concept of preventive health is often unfamiliar to people from developing countries. Most do understand the importance of immunizing their children because immunization campaigns have been carried out in the developing world since the era of smallpox eradication. But the rationale for obtaining regular Pap smears, mammograms, prostate examinations, and blood pressure checks is less obvious and usually has to be taught by the physician.

Intolerance of Side Effects and Expectations of Expeditious Wellness

Many, if not most, educated middle-class Americans can understand relatively benign side effects of treatment. The same cannot be said of many immigrants to the United States, however. Patients from Southeast Asia in particular are likely to sense an ominous incompatibility between themselves and their medication at the first hint of a side effect. I have rarely been able to talk them into not worrying about such things, and rather than try to overcome deep misgivings that may be rooted in a sense that balance is all or that one should not go against signs, I usually change the medication.

Possibly reflecting previous experience with treatments that were not efficacious, many patients from developing countries do not brook protracted therapy without results. As a rule of thumb, I assume I have just a couple of days to make foreign-born patients better, or I had better do some explaining or plan on losing the patient to another health care provider. This is not surprising if one considers that in some developing countries it is the custom to prescribe medications for only a day or two. Sometimes this practice is combined with a shotgun approach—spectacular polypharmacy with multiple antibiotics being common practice in many developing countries. In any case, conditions that require treatment for a sustained period—such as viral diarrhea or viral pneumonia—may warrant extra effort at patient education to ensure mutual understanding and compliance.

Somatization of Depression

Depressed patients who seek medical care for fatigue or other vague somatic complaints are familiar to all primary care physicians. Usually with a few diplomatically phrased questions, physicians can uncover the covert "blues" and confront them, sometimes with antidepressants. Few physicians are prepared by their own cultural backgrounds in the United States to handle the degree of resistance to discussing feelings that is seen in certain foreign-born patients. Many Islamic persons, for example, have been acculturated to believe that prayer is the appro-

priate strategy for dealing with sadness and that to do otherwise might be reprehensible. More pervasive than this, however, is the resistance of Vietnamese persons to discussing emotional feelings with non-family members. This can rarely be overcome, in my experience, but with effort, once depression is suspected—as it should be in most older and monolingual Vietnamese immigrants—patients can be persuaded to take antidepressants provided they do not experience side effects.

Health Belief Model and Beyond

About a decade ago, two new concepts were popularized in medical anthropology by the Harvard physician-anthropologist Arthur Kleinman. The first of these was the notion of "illness without disease."[11] The phrase refers to the somatization of unhappiness and depression by people who need, for whatever reason, to deny that they have emotional problems. It came to be recognized as a common phenomenon as physicians recalled how often in ambulatory primary care medicine they encountered illness without a diagnosable disease—some say 40% to 50% of the time.

The other perspective advocated by Kleinman was that patients' own conceptual models of disease had an important effect on their illness behavior.[12] This led to the insight that when patients seem to be behaving in a noncompliant manner, they are actually proceeding logically according to their own belief system.[13] A physician who understands their conceptual model will have a better chance of negotiating new and more healthful behaviors. Theoretically, also, the more physicians explain the biomedical model of the health problem, the more patients will understand why they should do what the physician suggests.

Anthropologic Methods for Physicians' Offices

In communicating with patients, knowing the precise details of specific medical beliefs and practices is less important than showing warmth, interest, and concern. Moreover, published taxonomies, lists, and tables of health beliefs, while useful,[14] are always going to have limitations and almost always must be qualified for individual patients. Thus, each physician can and should practice his or her own form of "anthropological research" to begin to understand a patient's conceptual world. Some possible ways to do this follow.

The Focus Group in the Waiting Room

Focus groups have made the transition from advertising to international public health, and they are also useful here in the multicultural United States. In the standard focus group, a number of people of the same age, sex, and status are brought together and the characteristics of a certain illness are explored—how it is recognized and by whom, how it is treated at home, and the like. This way of eliciting information enables the interviewer to get information from different people in a relatively short period of time. Physicians can gather appropriate persons together in their waiting rooms during the lunch hour or at the end of a day to form an informal group to learn about any aspect of patient behavior. For example, my students and I have used it effectively to learn about Mexican-born patients' attitudes toward their diabetes.

Projective Research Methods

Some of the medical anthropology methods most useful in field research are equally effective in an office setting. For example, I developed a technique that I call the clinical vignette.[15] These vignettes describe the symptoms of a person with a symptom complex well known to bioscience, such as chest pain radiating down the left arm in a middle-aged man. After relating the vignette to the interview subject, that person is asked what could be the cause of such a problem and how it should be treated. This approach helps physicians to learn about systems of belief and therapy that may be unfamiliar to them.

Another useful technique is displaying photographs to elicit patients' attitudes.[16] For example, if a physician wants to know what patients think about breast-feeding, smoking, or some other behavior, the physician can show them pictures of people from different socioeconomic strata in the patients' own culture and then ask which person is a smoker, which one is a breast-feeder, and so on. The kind of person identified and the patients' attitudes toward such a person help in understanding a patient's own behavior.

Participant-Observer Technique in the Office

What most people think of as anthropology—the bearded anthropologist living interminably amid a tribe, enduring privation, learning the language, and ultimately emerging from the jungle to publish an erudite ethnography—has come to be known as the "participant-observer" method. Being as unobtrusive as possible, the practitioner of this skill is expected to participate so fully in the culture (not only in ceremonies but in daily life) that people are no longer on their good behavior around him or her. In that way, an anthropologist can observe the most intimate truths of a society. Although time-consuming and laborious, this method has a persuasive power that transcends that of any mere interview or questionnaire.

Like a field anthropologist, a physician can, and should, become a participant-observer in the patient's world. Of course, no one would argue that people are at their most relaxed in a medical office or a hospital bed. But the goal is to be alert to glimpses of meaning, to try to understand the meaning of the illness to the patient, and above all to be sensitive to the little problems created by our medical system so that physicians can try to make it better. House calls and social activities in the communities of patients enable physicians to see the patients in their own milieus, and often our understanding and our appreciation of them are enhanced.[17]

Over and over again, one sees that understanding the social matrix of patients is crucial and that presenting ideas in a culturally sensitive way can make every difference in terms of clinical success or failure.[18] This is one

of the reasons that I prefer to think of medicine as quintessentially a social science. To paraphrase what used to be said about anatomy, all physicians make mistakes, but those who know their anthropology make fewer of them.

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AMERICAN ROULETTE

Forty-two and once again I am on my sick bed.
Third time in six and a half years: sarcoidosis, cancer,
now double intestinal obstruction:
a complication from the cancer surgery:
scar tissue sealed off the intestine
at two spots.
Another day or so and maybe
peritonitis, gangrene,
death.
A little emergency surgery and my guts are working again.

For the third time I have been caught
with insurance.

Lucky me:
For eighteen months I have hold-over insurance
from a City of Austin job:
no pre-existing condition clause.

One of these days I will have insurance
and all of those premiums will make no difference:
"It all stemmed from the cancer," they will say,

unless, of course, I am lucky.

JIM CODY©
San Antonio, Texas

Commentary

Integrity Versus Hypocrisy—That Delicate Balance
A Commentary on Humanity

LA VAL W. SPENCER, MD, *Ogden, Utah*

Life is a paradox, filled with ambiguities and dilemmas. A major concern for us is the relationship between integrity and hypocrisy. Is there not an absolute difference between these two traits? Or do we need an element of hypocrisy within our character development to support certain acts of integrity?

Most members of society seek to promote integrity and to eliminate hypocrisy. Yet can we eliminate hypocrisy completely? And if we happen to be successful in this endeavor, would this achievement jeopardize our very being? Is not hypocrisy a crucial part of our humanness and even our humaneness?

For example, we can strive to be as genuine and authentic as possible. We can even attempt complete honesty; and if great progress is realized, we could be transparent to society with nothing to hide or to keep secret. We would, however, soon be aware of the loss of our autonomy and privacy—even our possessions would not be safe.[1(p282)] Therefore, without secrecy and especially deception, the cornerstone of hypocrisy, we would lose the very ground of our existence.

Another challenge to integrity is curiosity. This trait can be of value when it motivates a person to attain greater knowledge and education. Yet common curiosity can tempt a person to violate integrity in exchange for the personal knowledge of others—information an ethical person would not strive to attain. For instance, there are many different types of electronic surveillance systems available today that can be used to monitor board rooms or private homes. A bright high school science student can reflect a laser beam from the windows of a building and monitor conversations. Computer hackers can penetrate information data systems about our health and financial records. Travel routes can be followed with the aid of a small transmitter concealed within an automobile. Satellite telescopes have the capability to survey action over a large area. Video cameras and one-way mirrors are used to record various private activities. Miniature recorders, concealed easily, can be used to monitor conversations. In addition, parabolic reflectors with sensitive microphones can record voices beyond 100 yards. The major restraint toward using this equipment maliciously is honor, the keystone of integrity.

Also associated with the quest for integrity is the pursuit of truth, to do good, and to cause no harm. There are conditions in life, however, that cannot tolerate disclosure. The truth would be most devastating; therefore, we avoid revealing our candid opinion about many sensitive circumstances. Moreover, we preclude harm by not communicating frivolous information about someone to another person—although the information may be true. Silence and a respect for the feelings of others is a reflection of discretion and cannot be violated without a loss of integrity. We walk a fine line because we also appreciate trust and integrity as the foundation stones of our social existence; yet, we know we cannot always be truthful.

In Book II of *The Republic*, Socrates attempted to persuade Glaucon that to practice justice is always better than to be unjust. Yet Glaucon insisted that "those who practice justice do so involuntarily and because they have not the power to be unjust . . . and are only diverted into the path of justice by the force of law . . . such a power as is said to have been possessed by Gyges, the ancestor of Croesus the Lydian."[2(p311)] This was the power of the ring of Gyges. Glaucon argued that anyone presented with this ring would use it to become invisible. He explained to Socrates[2(p312)]:

> Suppose now that there were two such magic rings, and the just put on one of them and the unjust the other; no man can be imagined to be of such an iron nature that he would stand fast in justice. No man would keep his hands off what was not his own when he could safely take what he liked out of the market, or go into houses and lie with any one at his pleasure, or kill or release from prison whom he would, and in all respects be like a God among men.

Is Glaucon right? Is there no one in society with the iron nature to withstand the temptation of such power? Would curiosity alone entice everyone to use the ring? Still a power near that of the ring of Gyges can be used today with the aid of concealed sophisticated electronic monitoring and surveillance equipment.

Another power, one that was not considered by Glaucon, is the capacity to unveil the thought processes of another person. The possession of this capability would allow anyone tremendous advantage and influence. A gift of this magnitude would be difficult to refuse. Yet the possibility of attaining this promethean power is starting to appear on the horizon.

(Spencer LW: Integrity versus hypocrisy—That delicate balance—A commentary on humanity. West J Med 1993; 159:614-615

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Today the electroencephalogram is used to record the brain electrical activity as it is influenced by many conditions. Scientists are now perfecting the magnetoencephalogram,[3] which is used to monitor and record the electromagnetic radiation of the brain at a distance. According to Roger Penrose, mathematician and physicist at the University of Oxford, "there is no doubt that electromagnetic phenomena have relevance to the workings of our brains."[4(p150)] As a consequence, there may be a means of intercepting and monitoring the thought processes.[5] This research is still in the experimental stage of development (B. Berger, "Mapping the Mindfields," *OMNI*, January 1992, pp 56-58). Yet with the exponential progress of computer science, cognitive psychology, neuroscience, and quantum physics,[4] we should not discount this power as a possibility in the future. How will we as physicians decide to use it? Are we indeed about to enter a new age, the Age of Truth?

There are many conditions in life that can test our integrity. Glaucon implied that there is an inverse correlation between integrity and temptation. Is Glaucon right? Can we be tempted beyond our sense of justice and integrity? Are we just only because we have not faced significant temptation? Socrates, however, did not agree with Glaucon. In the last book of *The Republic*, he said, "Let man do what is just, whether he have the ring of Gyges or not, and even if in addition to the ring of Gyges he put on the helmet of Hades."[2(p436)]

Thus, as we strive to attain genuine character traits, we value justice, candor, honesty, and honor in our relationships with members of society. We disdain those who have no compunction about lying, deception, or duplicity. To this end, we may think of Molière's play *The Misanthrope* in which Alceste is particularly critical of Philinte's polite effusiveness toward another[6(p869)]:

PHILINTE: But in polite society, custom decrees
That we show certain outward courtesies. . . .

ALCESTE: Ah, no! we should condemn with all our force
Such false and artificial intercourse.
Let men behave like men; let them display
Their inmost hearts in everything they say;
Let the heart speak, and let our sentiments
Not mask themselves in silly compliments.

PHILINTE: In certain cases it would be uncouth
And most absurd to speak the naked truth;
With all respect for your exalted notions,
It's often best to veil one's true emotions.
Wouldn't the social fabric come undone
If we were wholly frank with everyone?

Yet the ideal justice of Socrates or the rage for the genuine of Alceste is not found in our society as we know it today. We are, therefore, obliged to agree with Glaucon and Philinte and realize that the foundation stones of our integrity are bound together with the social fabric of deception and hypocrisy. Sissela Bok, writer and lecturer in ethics at Harvard Medical School, has said that there is an inherent "fundamental duplicity of the human being."[7(p x)] She added[7(p256)]:

> Nearly every kind of statement or action can be meant to deceive. Clearly intended lies—the most sharply etched forms of duplicity—have been in the foreground. . . . More marginal forms, such as evasion, euphemism, and exaggeration, have been close at hand, ready to prop up these lies or take their place. And all around have clustered the many kinds of deception intended to mislead without even marginally false statements: the changes of subject, the disguises, the gestures leading astray, all blending into the background of silence and inaction only sometimes intended to mislead.

Blaise Pascal certainly would have been in accord, as evidenced by his remark[8(p192)]:

> Human society is founded on mutual deceit; few friendships would endure if each spoke in sincerity and without passion. . . . [I] set it down as a fact that if all men knew what each said of the other, there would not be four friends in the world.

Our moral judgment is rarely without challenge. On the one hand, we strive for integrity. On the other, we must face hypocrisy because without deception we would sacrifice sensitivity and discretion. The truth can hurt.

Furthermore, if we were completely transparent, we could not maintain our autonomy, privacy, or possessions. The very ground of our being is contingent on some degree of deception. For this reason, we are obliged to sacrifice our candor by relying on secrets to protect our autonomy. Secrets cannot be protected without deceit, duplicity, or lying. Therefore, we cannot avoid hypocrisy—presenting to others the person we are not.

Still, we must maintain that delicate balance between integrity and hypocrisy to aver our existence. As a result, we are required to live in perpetual tension between these two conditions. The tension will increase as science and technology advance and the power for increased external secret surveillance and the power to intercept and monitor the internal thought processes becomes more available. As a consequence, the temptation to use these powers for our own advantage will bring about an ever-increasing challenge to our integrity and honor. The meaning of life, however, lies in its moral struggle.[9] And, as it has always been true, one must advance from tension to struggle, then to insight and wisdom. For this reason, the quest for complete personal honesty, authenticity, and justice will always be a noble and difficult endeavor.

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Editorials

Is Peptic Ulcer Disease an Infectious Disease?

THE IDENTIFICATION OF BACTERIA in human, as well as animal, stomachs dates back to the early part of this century; spiral bacteria were observed in patients with gastric cancer and peptic ulcer disease and in normal subjects.[1,2] The tide was shifted against a pathogenic role for gastric bacteria in the mid-1950s by E. D. Palmer, MD, who examined hundreds of gastric biopsy specimens and attributed the presence of gastric bacteria to salivary contamination.[3] The winds shifted back again in 1975 when Steer and Colin-Jones reported bacteria deep within the gastric mucosal layer in patients with gastric ulcer and postulated that these bacteria may alter mucosal resistance.[4] Further, Kornberg and Davies published a comprehensive review on gastric urease, identifying its origin from gastric bacteria.[5] Bacterial urease catalyzes urea to ammonia, thereby increasing the pH surrounding the bacteria and permitting bacteria to remain viable within the acidic gastric milieu. The seminal observation, however, was reported by Marshall and Warren in 1984 when they clarified the association between *Helicobacter pylori* (before 1989, referred to as *Campylobacter pylori*) and active chronic gastritis in human gastric mucosal biopsy specimens.[6]

Over the past three years more than 1,200 articles have addressed numerous aspects of *H pylori*, ranging from clinical issues (Is *H pylori* a major factor in the pathogenesis of nonulcer dyspepsia, peptic ulcer, or gastric cancer? Who to, and who not to, treat, and with what?) to fundamental studies of the cellular constituents of this unique microorganism (urease, lipase, a cytotoxic protein, adhesins). In addition, the medical community and the public are keenly aware of *H pylori* because of the flurry of articles in both the scientific literature and the public press. It is not uncommon to encounter a physician who asks, "What should I do with this patient of mine with dyspepsia or ulcer . . . should he or she be treated to eradicate *H pylori*? And, if so, what combination of drugs should be used?" Or a patient asks, "Could I have these potentially dangerous bacteria living in my stomach, and couldn't it make me more likely to develop an ulcer or even gastric cancer? Shouldn't I be checked to see if these bacteria are in my stomach?"

Elsewhere in this issue of the journal, Feldman and Peterson thoughtfully review a number of key issues regarding this ubiquitous bacterium.[7] They provide a well-balanced assessment of a large and complex body of literature. There remain a large number of both clinical and fundamental unanswered questions, however. As in other areas of medicine, there are the zealots who would recommend treating every patient who has *H pylori* and others who are reluctant to change from the current and effective acid-peptic treatment programs. I shall address four questions that are commonly raised regarding this organism.

Is Helicobacter pylori *the Cause or a Major Contributing Factor in Gastroduodenal Diseases?*

Helicobacter pylori is a definite cause of acute and chronic active gastritis, a cofactor in the pathogenesis and recurrences of peptic ulcer diseases (particularly duodenal ulcer), possibly a minor cofactor in the pathogenesis of gastric adenocarcinoma, and not established as a factor in nonulcer dyspepsia.

There is strong evidence that acute infection with *H pylori* can cause epigastric distress—nausea, vomiting, and epigastric pain—accompanied by acute gastritis.[8] This illness may be associated with transient achlorhydria and tends to resolve promptly; the bacteria will clear from some patients spontaneously, whereas in others chronic active gastritis will develop. As this self-limited illness has no clinical features that distinguish it from other forms of acute upper gastrointestinal distress and it resolves promptly, it is unlikely to be diagnosed as acute *H pylori* gastritis. Further, in patients with chronic active gastritis due to *H pylori*, eradication of the microorganism results in a prompt resolution of the acute inflammation and a slower regression of the chronic (mononuclear cell) inflammation.[9] It has not yet been established whether or not particular subtypes of *H pylori* are more predisposed than others to cause either acute or chronic active gastritis or the other sequelae of *H pylori* gastritis.

As reviewed by Feldman and Peterson, despite *H pylori*'s residing only in "gastric type" epithelia (the stomach or metaplastic tissue as in Barrett's esophagus or duodenal metaplasia), there is a definite association between *H pylori* infection and both duodenal and gastric ulcers. About 90% to 100% of patients with duodenal ulcers harbor *H pylori*, whereas about 70% to 90% of patients with gastric ulcers have gastric *H pylori*.[10-12] The lower prevalence of *H pylori* in patients with gastric ulcers is likely due to the ingestion of aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs). Although most patients with duodenal or gastric ulcers harbor *H pylori*, many more healthy people throughout the United States and the world are infected with *H pylori* yet remain free of ulcer disease. For example, although *H pylori* is extraordinarily common in Hispanics, African Americans, and in South America, Africa, and Southeast Asia, there is no evidence of an increased prevalence of ulcer disease in these subpopulations.[13] Feldman and Peterson and others suggest that the relative risk (or odds) ratio of ulcer developing in patients infected with *H pylori* is only about threefold or fourfold greater than for the general population.[7,14] This is in contrast to the substantially greater risk ratio of about 10 to 20 for the development of gastric ulcer in patients taking NSAIDs.[15]

Is *H pylori* the unidentified key factor that causes nonulcer dyspepsia? The answer at present appears to be "no." Because *H pylori* infection is so common, it is not surprising that a number of studies have failed to demon-

strate an increased prevalence of the infection in patients with nonulcer dyspepsia versus asymptomatic subjects, and the eradication of *H pylori* in patients with nonulcer dyspepsia does not consistently result in a resolution of the troublesome symptoms.[16,17] It is possible that in eradicating *H pylori*, a subpopulation of this heterogeneous group of patients may respond, but to date methods to define this subpopulation have yet to be established.

The medical community and the public are appropriately concerned about any possible cofactor in cancer pathogenesis. *Helicobacter pylori* has been incriminated as a predisposing factor to the development of adenocarcinoma of the gastric body and antrum, but not the gastric cardia.[18] In the United States, however, there has been a pronounced decrease in the incidence of ordinary gastric adenocarcinoma of the gastric corpus, but there has been a definite increase in that of carcinoma of the gastric cardia, the non-*H pylori*-associated tumors. The relative risk, or odds ratio, of cancer developing in *H pylori*-infected persons is only about 3.5.[18] As the incidence of gastric carcinoma is exceedingly low in the general population that harbors *H pylori*, there is no evidence at present to recommend the treatment of *H pylori*-infected patients to prevent the subsequent development of gastric adenocarcinoma.

How Does Helicobacter pylori *Contribute to the Development of Peptic Ulcer?*

The answers to how *H pylori* contributes to peptic ulcer development are not all in. As reviewed by Feldman and Peterson, a number of mechanisms whereby *H pylori* can cause injury to the mucosa have been postulated, including the fact that it contains large amounts of the enzyme urease (a cytotoxin) that results in ammonia production (also a cytotoxin) within the stomach. The organism also contains and releases chemotactic factors and cytotoxins (proteases, lipase, phospholipase A, and a "vacuolating" cytotoxin) that can cause mucosal injury, attract leukocytes to the area of injury that in turn can release additional cytokines, and thereby produce damaging superoxide radicals.[19] Because *H pylori* is capable of survival only in gastric mucosa, it remains unclear how it contributes to the pathogenesis of duodenal ulcer. Additional work is required to define the precise pathogenic mechanisms of *H pylori* in upper gastrointestinal tract diseases.

Who Should Be Treated to Eradicate Helicobacter pylori?

It is unusual for a day to go by without patients inquiring of their physicians whether or not they should be tested for *H pylori*; and, if they test positive, should therapy be prescribed? This is also an area of intense study, and, as for other questions about this bacterium, the answers are not all in. Some gastroenterologists recommend treating all patients who have duodenal ulcer with anti-*H pylori* therapy, as outlined by Feldman and Peterson, whereas others are content with the high healing rates (70% to 95% at 4 weeks) afforded by conventional antiulcer therapy (for example, histamine H_2-receptor antagonists, sucralfate, H^+/K^+-ATPase inhibitors, and the like). At present, there is suggestive but not unanimous evidence that triple-drug therapy plus H_2-receptor antagonists may expedite ulcer healing during the early healing stages (4 to 6 weeks) compared with H_2-receptor antagonists alone.[12,20] The early therapeutic gain is modest, about 15%. This slight advantage must be balanced by the increased drug costs; the inherent untoward side effects (about 30%) associated with the treatment of *H pylori*; the potential for the development of drug-resistant (particularly to metronidazole) strains of *H pylori*; and the observation that although most patients with duodenal ulcer tend to have recurrent disease, about 30% to 40% of patients have infrequent symptomatic recurrences that respond promptly to conventional ulcer treatment.[21]

Because the eradication of *H pylori* greatly diminishes the incidence of duodenal ulcer recurrence to less than 15% per year (versus about 75% recurrences in those not on any treatment program, and about 30% recurrences in those on daily prophylactic antiulcer therapy), there is unanimity that those patients with duodenal ulcer who have frequent recurrences (≥ two or three per year) or refractory or complicated duodenal ulcers should be treated to eradicate *H pylori*.[12,20] Similar guidelines apply to patients with gastric ulcer disease. Many gastric ulcers, however, are frequently secondary to aspirin or NSAID intake; discontinuing NSAIDs plus conventional antiulcer therapy is all that is required for ulcer healing and to prevent recurrences. Furthermore, those with first episodes of non-NSAID gastric ulcer heal well with conventional therapy. As with duodenal ulcer, those who have gastric ulcer recurrences, refractory ulcers, or gastric ulcer complications are appropriate candidates for treatment.[10] Finally, there is no indication at present that patients with nonulcer dyspepsia should be routinely treated with anti-*H pylori* therapy.[22]

What Information Regarding Helicobacter pylori *Should We Be Looking for in the Future?*

In patients with ulcer disease, cost-analysis comparisons of conventional or "on demand" antisecretory therapy versus triple-drug therapy are needed. Are the total costs (direct plus indirect costs) diminished by eradicating *H pylori* in all ulcer patients, or is this treatment limited to a specific identifiable subgroup? We need to know the effect of *H pylori* eradication on the incidence of ulcer complications. Does eradicating *H pylori* prevent recurrent peptic ulcer hemorrhage? If so, this would be a major advance. It is important to define the optimal therapy (greatest efficacy with the least untoward effects and lowest cost) for eradicating *H pylori*. Newer drug combinations, such as omeprazole plus amoxicillin or clarithromycin, are being contrasted to triple-drug therapy. Are they superior to current methods; do they have less untoward effects? At the fundamental level, it is important to identify the microorganism's and the host's factor(s) responsible for *H pylori* infection and the specific factors responsible for the progression from chronic ac-

tive gastritis to the development of other upper gastrointestinal tract diseases.

Clearly, important fundamental and clinically relevant information regarding *H pylori* and its relationship to gastroduodenal diseases will be forthcoming over the next few years. These results will likely have a major effect on our understanding of acid-peptic (or *H pylori*) diseases. At present, it is premature to disregard completely the contribution of acid and pepsin to peptic ulcer diseases.

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'Andropause'—Are Reduced Androgen Levels in Aging Men Physiologically Important?

GONADAL FUNCTION declines with increasing age in both women and men. At the time of menopause in women, there is a relatively abrupt and complete loss of ovarian function that results in markedly reduced estradiol and progesterone production and the cessation of ovulation. This profound reduction in ovarian function has substantial physiologic consequences, including an accelerated loss of bone mass and osteoporosis, hot flushes with accompanying sleep and behavioral changes, vaginal atrophy, and the loss of fertility. In contrast, men experience a more gradual and incomplete loss of testicular function with increasing age, resulting in reduced testosterone and sperm production. Although decreased spermatogenesis may contribute to the age-related reduction in male fertility, other factors such as a loss of interest in fathering children and diminished sexual function are probably the major causes of infertility in healthy elderly men. The physiologic importance of reduced testicular androgen production with aging, referred to by some investigators as "andropause," is unclear.

Numerous cross-sectional and limited longitudinal studies have found that beginning at about 50 years, serum total testosterone levels gradually and progressively decline with age, with lowest concentrations noted in those older than 70 years.[1-5] Because circulating testosterone is mostly bound to serum proteins and the concentration of the major testosterone binding protein, sex hormone-binding globulin, increases as men age, serum-free or bioavailable testosterone concentrations decline to a greater extent than total testosterone levels.[1-5] Furthermore, the normal circadian variation of testosterone levels observed in young men with peak concentrations in the morning is lost in elderly men.[6] As a result of these age-related changes, many elderly men have circulating testosterone levels below the normal range for young men.

Testosterone production by the testes is greatly reduced with aging, both in the basal state and in response to supraphysiologic luteinizing hormone or luteinizing hormone-like (human chorionic gonadotropin) stimulation.[7-10] Histologically, testes from elderly men have a reduced number and volume of Leydig cells.[11] The age-related reduction in the capacity of the testes to produce testosterone may result in a more severe and prolonged reduction of testosterone levels in response to external stresses, such as illness. Despite reduced testicular androgen secretion, serum testosterone levels are not reduced proportionately because testosterone clearance is also reduced with aging.[1]

The decreases in both serum total and free testosterone concentrations with aging are relatively small, and there is considerable variation in testosterone levels in men of all ages. Thus, a substantial number of elderly men have serum testosterone concentrations within the wide range of normal values observed in young men. Despite apparently normal testosterone levels in some elderly men, the pronounced decrease in basal and human chorionic gonadotropin-stimulated testosterone production with aging provides strong evidence for an age-related reduction in testicular Leydig cell function.

Age-related alterations in either active metabolism of testosterone or androgen receptor status may be important in determining androgen action in specific target tissues

and thus, the physiologic significance of reduced testosterone levels in those tissues in aging men. In various peripheral tissues and the testes, testosterone is converted to the active steroid hormone metabolites, estradiol or dihydrotestosterone, by aromatase and 5α-reductase enzymes, respectively. Despite reduced serum testosterone levels with age, most studies have not found notable age-related changes in serum estradiol and dihydrotestosterone concentrations in men.[2,3,5,7,9,10] These findings suggest that the activities of the aromatase and 5α-reductase enzyme may be increased in some tissues (such as fat and prostate, respectively). Age-related alterations in androgen receptor status have not been investigated extensively. Limited studies have suggested that androgen receptors are reduced in skin and increased in hyperplastic prostate of elderly men.[12,13]

The pronounced variation in serum testosterone levels between men together with the small number of men studied (especially younger than 30 or older than 70 years) may explain why some investigators did not find a major reduction in testosterone concentrations with age. Also, the failure to recognize that the circadian variability of testosterone levels observed in young men with peak levels occurring in the morning is lost in elderly men may explain why investigators who obtained blood specimens during the afternoon did not find a meaningful age-related decline in testosterone concentrations.[10,14]

Testicular function and, in particular, testosterone production are affected by a number of external factors, such as illness (with its associated stress response), medications, psychological state, obesity, exercise, socioeconomic condition (malnutrition associated with poor elderly), and life-style (alcohol or drug abuse). The presence of these factors may contribute to the notable variation in serum testosterone levels in both young and elderly men and a more pronounced age-related decline in testosterone concentrations observed in some studies.[3,5] It is worth emphasizing, however, that substantially decreased testosterone levels have also been reported in carefully screened, exceptionally healthy elderly compared with young men.[7] Because complicating conditions such as illness occur more often in elderly than in young men, serum testosterone levels in the general population of elderly men may be more profoundly suppressed than those in highly selected healthy older men.

Concomitant with the decline in serum testosterone levels, aging is associated with functional changes in a number of androgen-dependent body tissues. These include an age-related decline in sexual interest and function (including diminished libido and erectile function), a reduction in muscle mass and strength, a decrease in bone mass and an increase in fractures (osteoporosis), mood changes (including a decrease in the feeling of well-being and vigor), and alterations in sleep quality (reduced stage 3 and 4 and rapid-eye-movement sleep). These alterations contribute substantially to a functional decline in elderly men and are associated with considerable morbidity and a reduced quality of life. Because these changes occur in androgen target tissues, it is possible that the age-related decline in serum testosterone concentrations may contribute to reduced function.

In this issue of the journal, Swerdloff and Wang present an interesting and timely overview of the potential physiologic importance of reduced serum androgen levels in elderly men.[15] The known effects of severe androgen deficiency on psychosexual function, bone mass, and muscle mass and strength and of testosterone treatment in young hypogonadal men provide a rationale for the hypothesis that declining serum testosterone levels contribute to age-related physiologic alterations and a functional decline in these tissues.

Although severe androgen deficiency in elderly men probably results in physiologic changes similar to those found in young hypogonadal men, formal studies comparing the effects of severe androgen deficiency and responses to testosterone therapy in elderly compared with young hypogonadal men have not been done. Moreover, the physiologic importance of less severe degrees of androgen deficiency as observed in many elderly men remains unclear. In part, this is due to a generally poor understanding of the physiologic effects and mechanisms of the action of androgens on specific body functions and physiologic processes in both young and elderly men. It is likely that the dose-response effects of testosterone therapy will differ for different androgen-dependent physiologic processes. Furthermore, the role of active metabolites of testosterone (estradiol and dihydrotestosterone) and androgen-dependent anabolic hormones (such as growth hormone and insulinlike growth factor-I [IGF-I]) in mediating the actions of testosterone on specific target sites has not been clarified in either young or elderly men.

Although reduced serum androgen levels may contribute to age-related physiologic decline, clinically it is important to consider other factors that may play a role in the age-related functional decline of a particular organ. For example, factors such as reduced activity or immobility, nutritional deficiency, medications, alterations in vitamin D and calcium metabolism, excessive alcohol or cigarette use, diabetes mellitus, reduced growth hormone and IGF-I levels, and falls may all contribute to the reduction in bone mass and increase in the incidence of osteoporotic fractures with aging in men. From the standpoint of clinical management, it is also important to consider the effects of age-related physiologic changes on a patient's function and quality of life before embarking on therapeutic interventions.

To test the hypothesis that the reduction in serum testosterone levels with aging contributes to an age-related physiologic and functional decline, carefully controlled clinical trials to determine whether testosterone replacement therapy in elderly men can improve physiologic indices and function are needed. Initial studies investigating the effects of testosterone replacement therapy in a small number of healthy elderly men have been reported recently.

In a double-blind, placebo-controlled, crossover study, Tenover found that administering testosterone enanthate, 100 mg a week, for three months to 13 healthy elderly

men with low serum total and non–sex hormone-binding globulin bound testosterone levels (< 350 ng per dl and < 46 ng per dl, respectively) substantially increased lean body mass, reduced urinary hydroxyproline excretion, increased hematocrit, and decreased the total and low-density lipoprotein-cholesterol without changing high-density lipoprotein (HDL)-cholesterol levels.[16] Furthermore, 12 of the 13 men experienced behavioral changes (such as increased libido and feelings of well-being) that permited them to determine correctly whether they were receiving testosterone or placebo, despite the double-blind design of the study. No adverse effects or changes in prostate volume or postvoiding residual urine volumes were noted, but serum prostate-specific antigen levels increased slightly during testosterone treatment.

In a preliminary study, Morley and co-workers found that administering testosterone enanthate, 200 mg every two weeks, for three months to eight elderly hypertensive men with low serum bioavailable testosterone levels (<70 ng per dl) substantially increased hand-grip strength, serum osteocalcin levels, and hematocrit and decreased total cholesterol without changing HDL-cholesterol levels, compared with six untreated control subjects.[17]

Despite the short-term nature of these studies, testosterone treatment of mildly androgen-deficient elderly men had notable beneficial effects on lean body mass, muscle, and hematocrit and possibly on bone turnover and mood. No significant adverse clinical effects were noted.

As discussed by Swerdloff and Wang, when contemplating the use of testosterone replacement therapy in elderly men with mild androgen deficiency, the possible risks as well as benefits must be considered.[15] Of particular concern is the potential for testosterone treatment to stimulate benign or malignant prostate growth—benign prostatic hyperplasia and prostate carcinoma, respectively—and to reduce HDL-cholesterol levels that may result in an increased risk of coronary artery disease.

Larger and longer term studies are needed to determine both the risks and benefits of androgen replacement therapy in elderly men. To avoid the adverse effects of pharmacologic levels of androgens, a reasonable initial goal of therapy in elderly men is to restore normal testosterone levels. If the late evening to morning rise in serum testosterone levels is found to be physiologically important (for example, in maintaining normal sleep quality), it may also be useful to restore a normal circadian variation of serum testosterone levels. Such truly physiologic testosterone replacement is now possible and practical using recently developed transdermal testosterone delivery systems.[18] Recent evidence suggests an important role for dihydrotestosterone in stimulating benign prostatic hyperplasia. Because of concerns regarding the stimulation of prostate growth and the suppression of HDL levels during testosterone therapy, it may be useful to explore combining testosterone with a 5α-reductase inhibitor or to use an androgen preparation, such as 7α-methyl-19-nortestosterone that is aromatized but not 5α-reduced.[19]

In summary, aging in men is associated with a gradual and progressive decrease in serum testosterone levels and a decline in various physiologic functions. The physiologic importance of lower androgen levels in elderly men and their relationship to age-related decreases in sexual interest and function, muscle mass and strength, and bone mass and alterations in mood and sleep quality remain unclear. Clarification of the functional significance of reduced testosterone levels with aging ("andropause") awaits carefully designed, long-term, placebo-controlled trials to determine the possible risks and benefits of androgen replacement therapy in selected elderly men.

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Lessons From Hypersensitivity Pneumonitis

THE RESPIRATORY TRACT is one of three sites of interaction of humans with the environment (the other two being the skin and gastrointestinal tract). The 7,200 liters of air

inhaled daily by normal adults contains many substances that may injure the body. The inhalation of potentially toxic substances is usually followed by the removal or detoxification of these substances without injury to the person. This beneficial effect is achieved by various mechanical means—mucociliary escalator, cough, sneeze—and by detoxification by cells or cell products. Usually the immune consequences of inhaling antigens favor the detoxification and neutralization of foreign material—macrophages are activated, polymorphonuclear leukocytes and perhaps eosinophils are recruited, lymphocytes are sensitized—and are favorable to the host. At times, however, the immune consequences are themselves injurious, such as with asthma, allergic rhinitis, and hypersensitivity pneumonitis. Reasons for the occurrence of adverse effects in some healthy persons are diverse, but likely include differences of inherent characteristics. As an example, atopic asthma and allergic rhinitis are related to a genetic predisposition to form immunoglobulin (Ig) E antibodies following respiratory tract exposure to common aeroallergens.

Hypersensitivity pneumonitis, also known as allergic alveolitis, is a group of uncommon interstitial pulmonary diseases that offer important insights into the immunopathogenesis of more frequently encountered pulmonary disorders. The most common examples are farmer's lung disease and avian-associated hypersensitivity pneumonitis (such as pigeon breeder's disease and bird fancier's disease). As discussed by Kaltreider elsewhere in this issue,[1] the acute response to inhaling materials capable of causing hypersensitivity pneumonitis exhibits features of immune complex mediation, and the chronic disorder displays features of delayed-type hypersensitivity. Hypersensitivity pneumonitis represents the pulmonary diseases most clearly associated with immunologic events caused by inhaling known antigens. Clarification of the immune mechanisms of hypersensitivity pneumonitis may aid in devising innovative and more effective interventions in more common pulmonary diseases.

Several lessons are to be learned from hypersensitivity pneumonitis:

- The history remains the basis of diagnosis.
- Many lung diseases are immunologically mediated.
- Cells associated with delayed-type hypersensitivity are important determinants of immunoglobulin production, especially IgE.

Acute hypersensitivity pneumonitis presents as fever, dyspnea, hypoxemia, and radiologic changes of diffuse pulmonary interstitial nodules. This constellation of signs and symptoms is nonspecific, and the illness is often diagnosed as infectious pneumonia. Only a history of exposure to a particular environment four to six hours before the onset of symptoms, coupled with a past occurrence of similar episodes after the same exposure, allow the diagnosis to be considered. The presence of serum antibodies to the causative agent confirms previous sensitization. Lung biopsy is seldom necessary, but, when done, the specimen has characteristic pulmonary histologic features of chronic interstitial inflammation, often with poorly formed granulomata or bronchiolitis.

The chronic syndrome is more difficult to diagnose. The clinical presentation is that of pulmonary interstitial fibrosis with dyspnea and weight loss. Persistent questioning of the patient will disclose long-standing low-level exposure to likely agents. Serum antibody levels confirm exposure and sensitization. Avian antigens, especially in domestic situations, are most commonly involved.[2]

The acute response to the inhalation of offending material is characterized by neutrophilia found in bronchoalveolar lavage (BAL) fluid,[3] followed by interstitial granulomatous inflammation and $CD8^+$ lymphocytosis in the BAL specimen. Bronchoalveolar lavage lymphocytosis reflects exposure to offending material and may not be associated with evident pulmonary disease.[4] The presence of BAL $CD8^+$ lymphocytosis, although common, is dependent on the type of hypersensitivity pneumonitis and time since the last exposure.[5]

High-resolution computed tomographic scans of the chest show centrilobular nodules, ground-glass radiodensities, and emphysema. Hypersensitivity pneumonitis can be distinguished from sarcoidosis because nodules tend to be bronchocentric in hypersensitivity pneumonitis and follow bronchovascular bundles in sarcoidosis.

The treatment of acute disease with parenteral glucocorticosteroids accelerates the return of pulmonary function tests and gas exchange towards normal, but compared with untreated patients, does not alter pulmonary function at three months from the onset.[6]

These diseases carry substantial morbidity and mortality. Acute severe hypersensitivity pneumonitis rarely results in death. Long-term exposure more commonly results in progressive pulmonary fibrosis. A recent report from Mexico City describes a 30% mortality over five years in patients with pigeon breeder's disease.[2]

An unanswered question is the frequency of undiagnosed hypersensitivity pneumonitis in patients presenting with pulmonary interstitial fibrosis. Fully 10% of patients referred to the National Jewish Center in Denver, Colorado, with the diagnosis of interstitial fibrosis had pulmonary histologic features suggestive of hypersensitivity pneumonitis and usually a history of exposure to birds (T. King, MD, oral communication, July 1993). This emphasizes the necessity of obtaining a careful history, especially in patients with previous exposure to avian antigens.

Many pulmonary diseases, such as sarcoidosis and interstitial fibrosis, have features of immunologic reactivity that imply an immune pathogenesis, but in which the inciting antigen(s) has not been identified. Understanding the immunologic reactions that occur after the inhalation of known antigens would aid in the search for evidence of similar reactions in other pulmonary diseases with possibly similar mechanisms. Ultimately, the goal is the interruption of these immunologic reactions to ameliorate or prevent lung damage.

Although acute and chronic responses to antigen inhalation often occur in the same persons, they differ considerably and may represent two different responses to toxic material. The acute response apparently occurs in all persons with exposure to large amounts of antigen and is not associated with evidence of previous sensitization (serum antibody not present). In the case of farmers exposed to hay, this response has been called organic dust toxic syndrome. It is apparently more common than classic hypersensitivity pneumonitis in farming populations with exposure to the agents that cause farmer's lung disease and is characterized by transient fever, dyspnea, nonproductive cough, peripheral blood leukocytosis, and BAL neutrophilia. Unlike hypersensitivity pneumonitis, organic dust toxic syndrome is not associated with chest radiographic changes or permanent lung damage[7] and may represent immune complex-mediated lung injury as described by Kaltreider.[1] The distinction between acute hypersensitivity pneumonitis and organic dust toxic syndrome is not obvious, and it is possible that the former represents a recurrence of the latter in a person with previous exposure to antigen.

Unlike virtually all other pulmonary diseases, both hypersensitivity pneumonitis and organic dust toxic syndrome are more common in nonsmokers than in smokers. Cigarette smoking has many effects on the lung, and long-term cigarette smokers display some features of immune suppression. It is not clear which of the many effects of cigarette smoking lead to the observed protection against hypersensitivity pneumonitis.

Current concepts of delayed-type hypersensitivity suggest a key role for the T_H1 subset of $CD4^+$ cells in hypersensitivity pneumonitis. The expression of delayed-type hypersensitivity and of humoral immunity is a reflection of the activity of subtypes of $CD4^+$ T cells. T cells include $CD4^+$ (helper) and $CD8^+$ (suppressor or cytotoxic) subsets. $CD4^+$ cells can be divided into T_H1, T_H2, or T_H0 subsets by their patterns of cytokine secretion. T_H1 cells preferentially secrete interleukin (IL)-2, interferon gamma, and tumor necrosis factor-β, activate macrophages, and are responsible for delayed-type hypersensitivity reactions. In general, T_H1 cells do not provide help for immunoglobulin production. T_H2 $CD4^+$ cells secrete IL-4, IL-5, IL-10, and IL-13; provide help for immunoglobulin (particularly IgE) secretion; enhance eosinophil production, survival, and activity; and promote mast-cell maturation and proliferation. The development of either a predominant T_H1 or T_H2 response is dependent on many factors, including attributes of the antigen, the site of delivery, the adjuvant used, and the type of antigen-presenting cell encountered. Interestingly, cytokines secreted by one $CD4^+$ subset inhibit the development of the reciprocal subset. T_H0 cells secrete a mix of cytokines characteristic of both T_H1 and T_H2 cells.[8] Recent evidence from studies of animals indicates that $CD4^+$ cells can adoptively transfer experimental hypersensitivity pneumonitis.[9] The responsible cells have not yet been classified as T_H1, T_H2, or T_H0.

There is increasing evidence that common lung diseases once thought to be mediated by IgE or nonimmune mechanisms show delayed-type hypersensitivity. Asthma can be described as a chronic eosinophilic bronchitis of unknown cause associated with prominent changes of bronchial mucosal T-cell number, state of $CD4^+$ activation, and cytokine secretion. Asthma has many of the features of delayed-type hypersensitivity, such as the activation of bronchial mucosal lymphocytes and eosinophils.[10] Cytokines or messenger RNA for cytokines associated with delayed-type hypersensitivity reactivity, such as tumor necrosis factor-α, granulocyte-macrophage colony-stimulating factor, IL-1, IL-2, and IL-6, are present in BAL and in bronchial mucosal cells.[11]

Other common features of atopy—eosinophilia, mast cell hyperplasia, and increased levels of IgE—are indicative of T_H2 $CD4^+$ cell activity. Current research activity is directed toward deciphering the precise interrelations of T_H1, T_H2, and T_H0 $CD4^+$ cells in asthma.

The examination of hypersensitivity pneumonitis offers clinical insights into the diagnosis and immunopathogenesis of more common pulmonary diseases and illustrates current concepts of immune regulation.

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Eosinophilic Meningitis

To the Editor: We read with interest the article by Fuller and colleagues, "Eosinophilic Meningitis Due to *Angiostrongylus cantonensis*."[1] In their useful discussion of causes of cerebrospinal fluid eosinophilia, the authors omitted fungal infections of the central nervous system, particularly coccidioidal meningitis, as a cause of eosinophilic meningitis. We recently reported 3 cases of eosinophilic meningitis caused by coccidioidal meningitis,[2] and in a retrospective review of 27 cases of coccidioidal meningitis at Kern Medical Center in the southern San Joaquin Valley in California, we found that 9 (30%) patients had eosinophilic meningitis according to Kuberski's criteria of more than 10×10^6 per liter of eosinophils in the cerebrospinal fluid.[3] Accordingly, we concluded that meningitis caused by *Coccidioides immitis* is probably the most common cause of eosinophilic meningitis in endemic regions. As helminthic infections in general and *A cantonensis* specifically are unusual occurrences in the United States and are limited to rare cases among immigrants to this country, coccidioidal infection should also be considered.

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* * *

Dr Fuller Responds

To the Editor: I thank Drs Ismail and Arsura for bringing to my attention coccidioidal meningitis as a cause of eosinophilic meningitis. I read their recent article with interest.[1]

Coccidioides immitis is not found in Australia or the Pacific region, but most certainly should be considered in California as the most likely cause of eosinophilic meningitis.

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Posthypnotic Suggestion

To the Editor: I read with fascination the article, "Effect of Preoperative Suggestion on Postoperative Gastrointestinal Motility," by Disbrow and colleagues in the May 1993 issue.[1] It is a little disconcerting that the effort was not properly labeled as the effects of "posthypnotic suggestion" because that is certainly what took place. When a person's mind is concentrated—as it would be in a surgical setting—and he or she is given a suggestion that is accepted, that is called hypnosis.

I am bothered by the confusion in the article and in the editorial by Witte and Witte[2] over conscious versus subconscious thoughts that influenced the results. It was the subconscious acceptance of the suggestions and not conscious thoughts that provided the positive results. Hypnotic suggestions work only through subconscious control. After all, in the article on suggestions under anesthesia referred to by Witte and Witte,[3] the patients could not have had a conscious thought because they were unconscious.

Also, concerning the preoccupation with the Stanford Clinical Hypnosis Scale scores, everyone is suggestible to some degree through hypnosis. After all, who has not had the experience of driving on the freeway and suddenly becoming aware that they had driven 20 miles without realizing it? Their mind was superconcentrated in a hypnotic trance, and when they woke up, they had amnesia for the distance traveled.

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Drs Disbrow, Bennett, and Owings Respond

To the Editor: As Dr Tayloe has ascertained, the intervention used in our article could be called a posthypnotic suggestion. We feel this distinction is unnecessary, however. Whether patients are in a hypnotic state or not, the results of our study are the same. We did not use the term hypnosis because we did not induce a special state of consciousness. Instead, we incorporated the essential aspects of hypnosis that make it effective for altering physiologic functioning and that were already present in the hospital environment.

The intervention was based largely on the writings of Barber, who defined hypnosis as "a situation in which individuals are purposefully guided by carefully chosen words and communications (suggestions) to 'let go' of ex-

taneous concerns and to feel-think-imagine-experience ideas or events that they are rarely asked to experience."[1(p69)] Hypnosis is not described as a mysterious alternate state of consciousness. Instead, it is a situation in which the subject has a high expectancy or belief in the intervention, is highly motivated, and is focused on the intervention and free of distractions.

These criteria are routinely met in the preoperative hospital environment. Researchers or physicians are looked on by patients as authorities or experts, thus lending credibility to the intervention and instilling an expectancy of success in the patients. Because undergoing a surgical procedure is usually an emotional and physical crisis, patients are highly motivated to recover. An intervention taking place shortly before the procedure is likely to hold the interest and focus the attention of a patient. If properly administered, suggestions given by the physician shortly before an operation can produce positive results by mimicking the essential characteristics of hypnosis.

Because everyone is suggestible to some degree, we attempted to quantify—using the Stanford Hypnosis Clinical Scale—the influence of susceptibility to suggestion on the resolution of ileus. The Stanford Hypnosis Clinical Scale scores were not significantly correlated with the resolution of ileus, and there was no interaction between these scores and the experimental condition. Therefore, all patients can benefit from direct physiologic suggestions regardless of their susceptibility to suggestion.

In short, all patients seen by a physician in a preoperative setting are in a "hypnotic" state. The physician may choose to take advantage of this state and provide specific physiologic suggestions that patients can incorporate to hasten their recovery. Our study shows that patients will respond with a reduction in the duration of ileus.

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AIDS in India

To the Editor: Deborah Porterfield's personal reflections in the May 1993 issue[1] are certainly an eye opener to the policymakers of industrialized nations emphasizing the urgent need for redefining their global policy on the acquired immunodeficiency syndrome (AIDS). This article, however, puts physicians in developing nations in a bad light, depicting them as disinterested, misinformed, and apathetic. Having been associated with sexually transmitted diseases clinics in the Indian subcontinent, we think that such generalizations can be unfair to the scores of dedicated physicians in developing nations who deal with AIDS patients in the setting of scarce resources, with practically no backing at all from the international community. Given the cultural and ethnic diversity, socioeconomic impediments, and widespread illiteracy in these areas, the challenges faced by these physicians are at times insurmountable, which can be frustrating.

In a country like India where the population tops 1 billion, one needs to realize that the recent international funding of around $84 million[2] over a five-year period is too miniscule an amount even to initiate any worthwhile efforts to combat the epidemic. In fact, international financial support for AIDS prevention actually declined in the past year to around $110 million, roughly equivalent to a seventh of the public expenditure on AIDS in the United States.[3] Also, only 6% of global funding for the prevention of the human immunodeficiency virus (HIV) was spent in countries with 80% of the world's HIV-infected population.[3] Hence, we may assume that the faltering response from developed nations to assist global efforts against this epidemic has directly or indirectly resulted in the explosion of AIDS in developing nations like India. Physicians reading Porterfield's article may be misled into viewing the impact in the United States as minor compared with the global "time bomb" elsewhere. But one needs to realize that institutions in the United States are strong while the overall number of HIV-infected people in the US population is relatively small, around 0.4%.[3] Thus, creating a major distinction between countries can be unfair, and one primarily needs to blame this grossly inadequate global response for the current explosion of AIDS in heavily populated countries such as India, China, and Pakistan, which stand on the verge of national epidemics.

As rightly pointed out by Mann and colleagues: "A global ethic of caring has not been developed, and the global vision is dimming as HIV/AIDS is depicted as a 'developing country' problem. As a result, global leadership is declining."[3] It is time that all "world citizens" accept that AIDS is "our disease, not yours" and that industrialized nations like the United States take leadership roles in combating this common enemy, rather than making distinctions. Visitors like Porterfield need to perceive this aspect in their views about AIDS in developing nations.

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* * *

Dr Porterfield Responds

To the Editor: Drs Hussain and Vasireddi correctly highlight the need for a global response to the AIDS epidemic and for vastly increased support to developing countries. I propose that medical education programs for health care professionals would be an essential part of these efforts. In my limited experience in India, many physicians and nurses did not feel that AIDS was an important health care issue for India. At the same time, in my article I attempted to communicate how inspired I was by the HIV research and clinical groups I met in Madras, Vellore, and Delhi. Certainly, fear and misunderstanding about HIV exist among physicians and citizens in every country; this represents only one of many battles to be fought.

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Gadolinium Nonradioactivity

To the Editor: I read with amazement in the July 1993 issue in the epitome "Preserving Hearing in Acoustic Neuroma Removal," that gadolinium is radioactive.

We have enough difficulties convincing patients to climb into magnetic resonance imaging (MRI) units without invoking radioactivity.

Gadolinium is a paramagnetic substance that produces shortening of the T1 value of water when it can interact with water. This results in increased signal intensity on T1-weighted images. There is no radioactivity involved. In fact, all energies used to do MRI studies are room temperature energies. No high-energy physics is involved in the process.

I think the record needs to be set straight on this critical issue.

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* * *

Dr Johnson Responds

To the Editor: Our epitome includes an editing error, appropriately pointed out by Dr Solomon, stating that gadolinium technique of enhancement for MRI scanning involves radioactivity. This is clearly an error and should read "nonradioactive."

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The Editors are pleased to receive letters commenting on articles published in the journal in the past six months, as well as information or short case reports of interest to our readers. ALL MATERIAL SUBMITTED FOR CONSIDERATION MUST BE DOUBLE-SPACED. Letters NO LONGER THAN 500 WORDS are preferred. An original typescript and one copy should be submitted. All letters are published at the discretion of the Editors and subject to appropriate editing. Those of a scientific nature will be peer reviewed. Authors should include information regarding conflict of interest, when appropriate ("I warrant that I have no financial interest in the drugs, devices, or procedures described in this letter"). Most letters regarding a previously published article will be sent to the authors of the article for comment. Authors of accepted letters will have an opportunity to review the edited version before publication.

Lessons From the Practice

Defeat

ERIC G. ANDERSON, MD, *San Diego, California*

These events happened more than 30 years ago in rural Texas, yet they come to mind as easily as my telephone number.

The patient rose in his bed to thank me for coming. I waved him back onto his pillow as I swept my eyes around the room. I saw the enamel bowl, the wet clothes, and the aspirin bottle that meant vomiting, fever, and pain, probably headache, to a country physician.

He was flushed and had a slight cough.

He was 51 years old, and in three days he would be dead.

"Hi, Mr Sanford, I'm Eric Anderson. What can I do for you?" I said. He changed his position in bed with some difficulty and said, "I'm just so danged tired. I think if I could just get rid of that I'd be back to normal."

There was not much to go on. He had vomited once. Headache. He had had a temperature with chills for a few days. No urinary symptoms. No loss of appetite. Examination did not help much either. He was a bit dry but nothing else.

He was like the 20 or 30 patients I had seen with gastroenteritis in the past few days during that hot Texas summer, and yet something bothered me: His symptoms had lasted a full week, and he was not usually one to call me without reason. He probably was no different from all the others, but a wise old physician once told me, "The best lab test is the second visit." So I spoke to his wife by the bedside, "Mrs Sanford, I'll come back tomorrow. Could you get him to drink more fluids? He's a bit dehydrated, and tomorrow I'll want a urine specimen. OK?"

When I returned, I found my patient on his porch, rocking in a chair, reading the local newspaper. It was the eighth day of his illness. I nodded to him with a smile. He waved the newspaper at me in reply and called out, "Hi, Doc. Just checking to make sure my obituary isn't in the paper!"

He laughed at my expression and looked over at his wife for her approval. I caught a flash of color in his eyes as he glanced away.

"Come out into the daylight, Mr Sanford," I said, more abruptly than I had meant. Surprised, he raised his eyebrows, and I saw it again. He was jaundiced.

"Let's get you back in bed and see what's going on," I said. His liver was ever so slightly tender. I asked the usual questions. Had his urine been dark? Yes, today. As dark as Coca Cola? No. Had his stools changed in color? Well, yes, no, he could not say. Was his skin itchy? No. Did he feel depressed? He laughed. No.

"Look, Doc," he said. "I feel better. What's the big deal?"

"The deal is that you've got a sick liver and that *can* be a big deal," I said. "You probably have infectious hepatitis. I'll draw blood now, and I'd like you to get someone to take it up to a lab in Duffield. I'll know within two days whether your family needs to take gamma globulin shots."

I left, relieved that things were becoming more tidy. "Call me if there's any change," I said on the way out. "And remember, all of you, wash your hands when you go to the toilet and before you eat."

Wash your hands. In retrospect, it was useless advice. The telephone rang the next day. Lucy, the receptionist, picked it up. I saw her face change. It could have been any one of several hundred families calling, but I knew it was the Sanfords.

"Something terrible's happened at the Sanfords'," Lucy said. "They need you right away."

I took off at breakneck speed, my thoughts going even faster. What could have gone wrong? What could I have missed? My car skidded to a stop outside the house with gravel still striking the picket fence as I ran up the path. I opened the door without knocking and burst into the bedroom. My God, I thought, he's dead! He lay on his back with eyes rolled up, and I could see it: the yellow in his eyes was flecked with red. I flopped onto his bed and leaned over him. The yellow was flecked with red! He had leptospirosis.

I felt a tightness in my chest. My throat was dry. I could hardly swallow. Two years out of medical school, I could smell the defeat and taste the fear.

His neck was stiff; there was a crust of blood at his nostril; and there was blood in the paper tissues that lay in the wastepaper basket beside him. His wife came in. "Call the ambulance," I said, my voice tremulous. "We need them fast."

He waited until I put down my stethoscope, then turned his head slowly with great dignity and said to me, "Well, Doc?"

"You've got leptospirosis," I told him. "A form of jaundice. You pick it up from rats' urine or infected animals. Sewers, skunks, raccoons."

He thought. Well, he had been under a house doing

(Anderson EG: Defeat. West J Med 1993; 159:626-627)

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plumbing repairs, and the sand had been wet. There was a clatter outside and a banging of screen doors as the ambulance men came in. I seized one by the elbow and said, "I've never asked you to drive fast before—this time, I'm asking you. OK?"

He looked down at his elbow in both discomfort and surprise, then they went off, swaying through the narrow doorway, staggering under their burden because Mr Sanford was not a light man. I took Mrs Sanford aside to explain what was going on.

The ambulance driver came back and took me into a corner. "Doc, he was speaking to me as we fixed him up in the ambulance," he said. "But I've just checked him again. And—and he's dead."

There was not a great deal known then about leptospirosis. In dismay, I called a medical school in Houston and asked them to send me the latest literature. I was drained by this defeat, one of my first deaths, especially in a man relatively young and previously so healthy. After some days the medical literature came. Late that night I spread the material in front of me on the kitchen table and started reading.

"The mortality is 56% in patients over the age of 50 years," I read, "higher if jaundiced. Antibiotics may be of value but data are conflicting. There is general agreement that antibiotics administered after the fifth day have no beneficial effect.

"Morbidity is high as is mortality," I read. "Not uncommonly the patient dies of sudden heart failure as he steps into the ambulance."

As he steps into the ambulance. I breathed the words and wearily took off my tie and headed for the bedroom. I saw my reflection in the mirror and did not recognize my face.

Promises Broken

FAZLUR RAHMAN, MD, *San Angelo, Texas*

Mrs Walton was my irreverent patient, yet we had been friends for nine years. She had a fine sense of humor and joked about being an ancient character of 93 years. Whether her body was weak or strong, her mind was always sharp. Despite her illnesses—she suffered from refractory anemia requiring intermittent packed cell transfusions—our encounters were pleasant. She had come so many times that we both knew what to expect.

Mrs Walton had been widowed for more than 30 years and had lived alone in her own home. Then anemia and a heart ailment limited her, and for the past ten years, she had been living in an apartment of a retirement high-rise.

"I have made a lot of friends, but I lose them so often. I make new friends, try not to worry about the ones who are gone," she told me many times. "Sometimes I just confine myself to my room. There is nobody to talk to. There are plenty of people there, but few have any mind left to converse. Their degradation is what bothers me most," she confided.

Once in a while she put me on the spot. "You will not dump me in a nursing home, will you?" she would ask me with a broad smile.

"Oh, no, Mrs Walton, I won't do such a thing. You will stay in your apartment as long as you want" was my usual answer. Time and again, she thanked me for the reply she wanted to hear.

One time she came in with anorexia and dehydration, looking like a piece of dry wood. She had taken too many digoxin tablets, one of her many medications, and toxicity developed. We stopped as many of her pills as we could.

After her recovery, Mrs Walton returned to her apartment once more, but four weeks later she was brought to me again. She had been standing in line at the cafeteria when her right arm suddenly became weak and her right leg went limp.

Mrs Walton now had become difficult to handle. Nobody could pass by her room at the hospital without being called in and asked the same questions again and again. She pressed the nurses' call button frequently. She was angry and stubborn. When she fell down twice in one night, the nurses put a bed restraint on her. She was furious at me when I saw her on rounds the next morning.

"Andy will get you," she screamed at me. "And I'll get my lawyers to teach you a lesson." Andy was her late husband.

She was struggling violently to get out of the restraint. I could see the bruises on her elbows. She had torn off her clothes. She was always particular about her appearance, but now she looked disheveled and wild.

A computed tomographic scan of her head showed a meningioma that was responsible for the changes in her behavior. Under ordinary circumstances, the lesion could be successfully resected. In her case, however, we left the

(Rahman F: Promises broken. West J Med 1993; 159:627-628)

From the Section of Hematology and Oncology, Angelo Community Hospital and West Texas Medical Associates, San Angelo, Texas.
Reprint requests to Fazlur Rahman, MD, Section of Hematology and Oncology, West Texas Medical Associates, 3555 Knickerbocker Rd, San Angelo, TX 76904.

tumor alone. An operation would not add to the quality of her life. Palliative treatment with dexamethasone reduced her cerebral edema and briefly cleared her mind.

Her daughter and son-in-law had done their best to help her in the past, but they were in their early 70s and in ailing health themselves. Now, to compound the problem, the management of her apartment refused to take her back. A nursing home for her was our only choice. The daughter asked me to break the news to her.

All my intimacy with Mrs Walton did not save me from her anger.

"Mrs Walton, the apartment people may not be able to help you any more," I blurted out. I did not have the heart to tell her that she was not welcome there any longer.

"They better, I have lived there for ten years, and I have always paid my bills," she shot back.

Her younger brother was already in a nursing home where we wanted to admit her. We pleaded for days to get her consent.

"What about all those promises you made, Doctor? Didn't you say I could stay in my apartment as long as I wanted? Do you have a short memory?" she demanded.

She did not give an inch—if I sent her out against her will, she would manage to get sick and come back right away.

I had already received subtle pressure from the hospital. The Utilization Review Committee had checked her records. I was keeping her in the hospital for "custodial" care, and the hospital was losing money. I must do something for her quick "disposition."

She reluctantly agreed to go the next day. In the morning, the head nurse called to tell me that Mrs Walton had stumbled in her room and fractured her right elbow.

Finally, a few days later she departed, but not before she chided me for my indiscretions. I had to make a promise—a promise I knew I could not not keep—that if she did not like the nursing home, I would bring her back.

Though I understood Mrs Walton's rage and frustration, I was unable to change her circumstances. These scenes and predicaments will be more and more common in the world of our parents and grandparents as our loved ones age.

* * *

"Lessons From the Practice" presents a personal experience of practicing physicians, residents, and medical students that made a lasting impression on the author. These pieces will speak to the art of medicine and to the primary goals of medical practice—to heal and to care for others. Physicians interested in contributing to the series are encouraged to submit their "lessons" to the series' editors.

JONATHAN E. RODNICK, MD
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Assistant Editors

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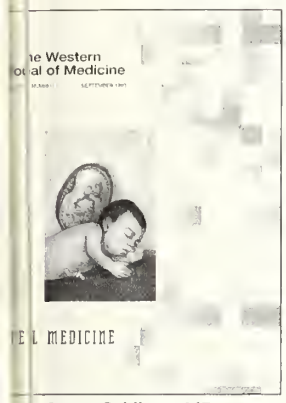
SEPTEMBER 1993



James Goldberg, MD
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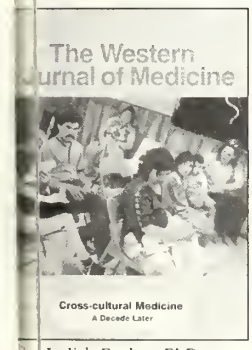

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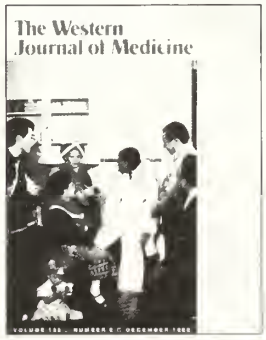

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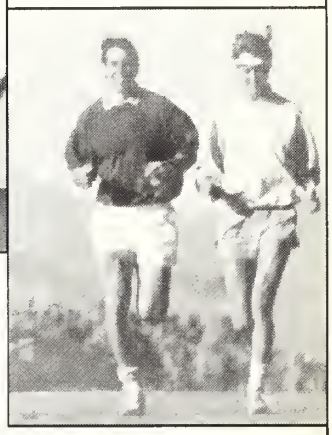

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BC/BE FAMILY PRACTICE, INTERNAL MEDICINE physicians with Emergency or Urgent Care experience needed to provide double coverage at the San Bernardino Community Hospital Emergency Department. This busy Emergency Department has 17 stations and a four-bed fast track program. Paid malpractice. Contact Wendy Brown, Emergency Physicians' Medical Group, 120 Montgomery, Ste 1000, San Francisco, CA 94104; (415) 989-1242.

NORTHERN CALIFORNIA HOSPITAL seeking a BC/BE Internist to staff its new satellite medical clinics. Assistance is available in establishing a practice. Net income guarantees are open including support for office staff and required equipment. Contact Margaret Ward, Redbud Community Hospital, PO Box 6720, Clearlake, CA 95422; (707) 994-6486, ext 128.

ROCKY MOUNTAIN WEST AND SOUTHWEST NEED PHYSICIANS. All specialties needed. Urban, rural, solo, group opportunities, all close to mountain recreation. Call Rita Longino at (800) 279-5267 or FAX CV to (800) 467-1246 or send CV to WHS, PO Box 2107, Corrales, NM 87048-2107.

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ORTHOPEDIC SURGEONS. Orthopedic Surgeon for a very busy Orthopedic service in a 223-bed teaching hospital with residencies in General Surgery, Internal Medicine, OB/GYN, and Family Practice. Should be BC/BE. Experience in arthroscopy preferred. Salary and compensation plan negotiable depending on experience. Hospital located in beautiful northern San Joaquin Valley close to major cities and skiing areas. Please submit CV and references or contact Nathaniel Matolo, MD, Chief of Surgery, San Joaquin General Hospital, PO Box 1020, Stockton, CA 95201; phone (209) 468-6600. AA/EOE.

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(Continued on Page 634)

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(Continued from Page 633)

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(Continued on Page 636)

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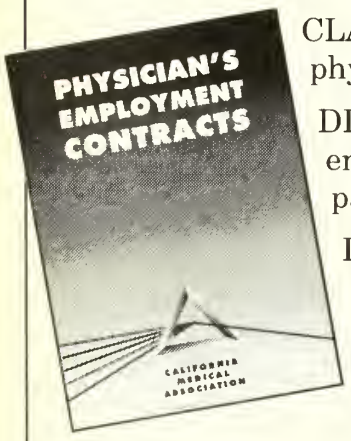

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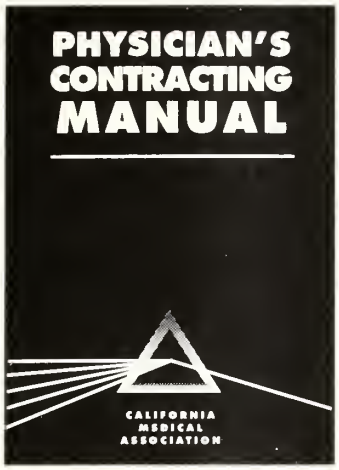

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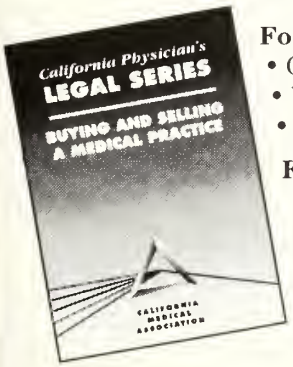

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California Medical Association–PO Box 7690, San Francisco 94120-7690. (415) 541-0900. Annual Meeting: March 18-23, 1994, Disneyland Hotel, Anaheim.

Colorado Medical Society–PO Box 17550, Denver 80217-0550. (303) 779-5455. Annual Meeting: September 7-11, 1994, Aspen.

Hawaii Medical Association–1360 S Beretania, Honolulu 96814. (808) 536-7702. Annual Meeting: 1994, date and location to be announced.

Idaho Medical Association–305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888. Annual Meeting: July 28-30, 1994, Sun Valley.

Montana Medical Association–2012 11th Ave, Suite 12, Helena 59601. (406) 443-4000. Annual Meeting: September 29-October 1, 1994, Holiday Inn, Great Falls.

Nevada State Medical Association–3660 Baker Lane, Reno 89502. (702) 825-6788. Annual Meeting: April 21-24, 1994, Coronado, California.

New Mexico Medical Society–7770 Jefferson NE, Suite 400, Albuquerque 87109. (505) 828-0237. Annual Meeting: May 5-7, 1994, Society Office, Albuquerque.

Utah Medical Association–540 E Fifth South, Salt Lake City 84102. (801) 355-7477. Annual Meeting: September 21-24, 1994, University Park Hotel, Salt Lake City.

Washington State Medical Association–900 United Airlines Bldg, 2033 6th Ave, Ste 1100, Seattle 98121. (206) 441-9762. Annual Meeting: September 22-24,1994, Wenatchee.

Wyoming Medical Society–PO Drawer 4009, Cheyenne 82003-4009. (307) 635-2424. Annual Meeting: June 9-11, 1994, Jackson Lake Lodge, Moran.

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For The Treatment Of Reflux Disease

WHEN ACID REFLUX ERUPTS

antac® 150 Tablets
ranitidine hydrochloride)
antac® 300 Tablets
ranitidine hydrochloride)
antac® Syrup
ranitidine hydrochloride)

BRIEF SUMMARY

he following is a brief summary only. Before prescribing, see complete prescribing information in antac® product labeling

NDICATIONS AND USAGE: Zantac® is indicated in.
Short-term treatment of active duodenal ulcer.
Maintenance therapy for duodenal ulcer patients at reduced dosage after healing of acute ulcers.
The treatment of pathological hypersecretory conditions (e.g., Zollinger-Ellison syndrome and systemic mastocytosis).
Short-term treatment of active, benign gastric ulcer
Treatment of gastroesophageal reflux disease (GERD)
Treatment of endoscopically diagnosed erosive esophagitis.
Concomitant antacids should be given as needed for pain relief to patients with active duodenal ulcer; active, benign gastric ulcer; hypersecretory states; GERD; and erosive esophagitis

ONTRAINDICATIONS: Zantac® is contraindicated for patients known to have hypersensitivity to the rug or any of the ingredients

RECAUTIONS: General: 1. Symptomatic response to Zantac® therapy does not preclude the presence of gastric malignancy.
Since Zantac is excreted primarily by the kidney, dosage should be adjusted in patients with impaired renal function (see DOSAGE AND ADMINISTRATION). Caution should be observed in patients ith hepatic dysfunction since Zantac is metabolized in the liver
Rare reports suggest that Zantac may precipitate acute porphyric attacks in patients with acute porphyria. Zantac should therefore be avoided in patients with a history of acute porphyria
aboratory Tests: False-positive tests for urine protein with Multistix® may occur during Zantac therapy, and therefore testing with sulfosalicylic acid is recommended
rug Interactions. Although Zantac has been reported to bind weakly to cytochrome P-450 *in vitro*, commended doses of the drug do not inhibit the action of the cytochrome P-450-linked oxygenase zymes in the liver. However, there have been isolated reports of drug interactions that suggest that ntac may affect the bioavailability of certain drugs by some mechanism as yet unidentified (e.g., a -dependent effect on absorption or a change in volume of distribution)
Increased or decreased prothrombin times have been reported during concurrent use of ranitidine d wartarin. However, in human pharmacokinetic studies with dosages of ranitidine up to 400 mg r day, no interaction occurred; ranitidine had no effect on wartarin clearance or prothrombin time. e possibility of an interaction with warfarin at dosages of ranitidine higher than 400 mg per day has t been investigated
rcinogenesis, Mutagenesis, Impairment of Fertility: There was no indication of tumorigenic or rcinogenic effects in life-span studies in mice and rats at dosages up to 2,000 mg/kg per day
Ranitidine was not mutagenic in standard bacterial tests (*Salmonella, Escherichia coli*) for mutaicity at concentrations up to the maximum recommended for these assays
In a dominant lethal assay, a single oral dose of 1,000 mg/kg to male rats was without effect on the tcome of two matings per week for the next 9 weeks
egnancy: ***Teratogenic Effects: Pregnancy Category B:*** Reproduction studies have been performed rats and rabbits at doses up to 160 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to Zantac. There are, however, no adequate and well-controlled udies in pregnant women. Because animal reproduction studies are not always predictive of human sponse, this drug should be used during pregnancy only if clearly needed
rsing Mothers: Zantac is secreted in human milk. Caution should be exercised when Zantac is administered to a nursing mother
diatric Use: Safety and effectiveness in children have not been established
e in Elderly Patients: Ulcer healing rates in elderly patients (65-82 years of age) were no different m those in younger age-groups. The incidence rates for adverse events and laboratory abnormalis were also not different from those seen in other age-groups.
VERSE REACTIONS: The following have been reported as events in clinical trials or in the routine nagement of patients treated with Zantac®. The relationship to Zantac therapy has been unclear in ny cases. Headache, sometimes severe, seems to be related to Zantac administration.
ntral Nervous System: Rarely, malaise, dizziness, somnolence, insomnia, and vertigo. Rare cases eversible mental confusion, agitation, depression, and hallucinations have been reported, predomntly in severely ill elderly patients. Rare cases of reversible blurred vision suggestive of a change in ommodation have been reported. Rare reports of reversible involuntary motor disturbances have en received
rdiovascular: As with other H_2-blockers, rare reports of arrhythmias such as tachycardia, bradydia, atrioventricular block, and premature ventricular beats.
strointestinal: Constipation, diarrhea, nausea/vomiting, abdominal discomfort/pain, and rare rets of pancreatitis
patic: In normal volunteers, SGPT values were increased to at least twice the pretreatment levels in

Zantac® 150 and 300 (ranitidine hydrochloride) Tablets
Zantac® (ranitidine hydrochloride) Syrup

6 of 12 subjects receiving 100 mg q.i.d. intravenously for 7 days, and in 4 of 24 subjects receiving 50 mg q.i.d. intravenously for 5 days. There have been occasional reports of hepatitis, hepatocellular or hepatocanalicular or mixed, with or without jaundice. In such circumstances, ranitidine should be immediately discontinued. These events are usually reversible, but in exceedingly rare circumstances death has occurred.
Musculoskeletal: Rare reports of arthralgias and myalgias
Hematologic: Blood count changes (leukopenia, granulocytopenia, and thrombocytopenia) have occurred in a few patients. These were usually reversible. Rare cases of agranulocytosis, pancytopenia, sometimes with marrow hypoplasia, and aplastic anemia and exceedingly rare cases of acquired immune hemolytic anemia have been reported.
Endocrine: Controlled studies in animals and man have shown no stimulation of any pituitary hormone by Zantac and no antiandrogenic activity, and cimetidine-induced gynecomastia and impotence in hypersecretory patients have resolved when Zantac has been substituted. However, occasional cases of gynecomastia, impotence, and loss of libido have been reported in male patients receiving Zantac, but the incidence did not differ from that in the general population
Integumentary: Rash, including rare cases suggestive of mild erythema multiforme, and, rarely, alopecia
Other: Rare cases of hypersensitivity reactions (e.g., bronchospasm, fever, rash, eosinophilia), anaphylaxis, angioneurotic edema, and small increases in serum creatinine

OVERDOSAGE: There has been limited experience with overdosage. Reported acute ingestions of up to 18 g orally have been associated with transient adverse effects similar to those encountered in normal clinical experience (see ADVERSE REACTIONS). In addition, abnormalities of gait and hypotension have been reported.
When overdosage occurs, the usual measures to remove unabsorbed material from the gastrointestinal tract, clinical monitoring, and supportive therapy should be employed.
Studies in dogs receiving dosages of Zantac® in excess of 225 mg/kg per day have shown muscular tremors, vomiting, and rapid respiration. Single oral doses of 1,000 mg/kg in mice and rats were not lethal. Intravenous LD_{50} values in mice and rats were 77 and 83 mg/kg, respectively.

DOSAGE AND ADMINISTRATION: (See complete prescribing information in Zantac® product labeling.)
Active Duodenal Ulcer: The current recommended adult oral dosage is 150 mg or 10 mL (2 teaspoonfuls equivalent to 150 mg of ranitidine) twice daily. An alternative dosage of 300 mg or 20 mL (4 teaspoonfuls equivalent to 300 mg of ranitidine) once daily at bedtime can be used for patients in whom dosing convenience is important. The advantages of one treatment regimen compared to the other in a particular patient population have yet to be demonstrated.
Maintenance Therapy: The current recommended adult oral dosage is 150 mg or 10 mL (2 teaspoonfuls equivalent to 150 mg of ranitidine) at bedtime
Pathological Hypersecretory Conditions (such as Zollinger-Ellison syndrome): The current recommended adult oral dosage is 150 mg or 10 mL (2 teaspoonfuls equivalent to 150 mg of ranitidine) twice a day. In some patients it may be necessary to administer Zantac® 150-mg doses more frequently. Dosages should be adjusted to individual patient needs, and should continue as long as clinically indicated. Dosages up to 6 g per day have been employed in patients with severe disease.
Benign Gastric Ulcer: The current recommended adult oral dosage is 150 mg or 10 mL (2 teaspoonfuls equivalent to 150 mg of ranitidine) twice a day
GERD: The current recommended adult oral dosage is 150 mg or 10 mL (2 teaspoonfuls equivalent to 150 mg of ranitidine) twice a day
Erosive Esophagitis: The current recommended adult oral dosage is 150 mg or 10 mL (2 teaspoonfuls equivalent to 150 mg of ranitidine) four times a day
Dosage Adjustment for Patients With Impaired Renal Function: On the basis of experience with a group of subjects with severely impaired renal function treated with Zantac, the recommended dosage in patients with a creatinine clearance less than 50 mL per minute is 150 mg or 10 mL (2 teaspoonfuls equivalent to 150 mg of ranitidine) every 24 hours. Should the patient's condition require, the frequency of dosing may be increased to every 12 hours or even further with caution. Hemodialysis reduces the level of circulating ranitidine. Ideally, the dosing schedule should be adjusted so that the timing of a scheduled dose coincides with the end of hemodialysis

July 1992
2130B

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DIVISION OF GLAXO INC

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Glaxo Pharmaceuticals, Research Triangle Park, NC 27709

Zantac® Syrup
Manufactured for Glaxo Pharmaceuticals, Research Triangle Park, NC 27709
by Roxane Laboratories, Inc., Columbus, OH 43216

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Zantac® Tablets

ranitidine HCl/Glaxo 150 mg tablets bid

For The Treatment Of Reflux Disease

WHEN ACID REFLUX ERUPTS

Please see Brief Summary of Prescribing Information on adjacent page.

Glaxo/ Roche

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VASERETIC® 10-25 *Next*
Enalapril Maleate-Hydrochlorothiazide

Dosage must be individualized; the fixed combination is not for initial therapy.

Evaluation of the hypertensive patient should always include assessment of renal function.

For a Brief Summary of Prescribing Information, see adjacent pages.

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VASERETIC®
(ENALAPRIL MALEATE-HYDROCHLOROTHIAZIDE)

USE IN PREGNANCY: When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, VASERETIC (Enalapril Maleate-Hydrochlorothiazide) should be discontinued as soon as possible. See WARNINGS, *Fetal/Neonatal Morbidity and Mortality*.

CONTRAINDICATIONS: VASERETIC is contraindicated in patients who are hypersensitive to any component of this product and in patients with a history of angioedema related to previous treatment with an angiotensin converting enzyme inhibitor. Because of the hydrochlorothiazide component, this product is contraindicated in patients with anuria or hypersensitivity to other sulfonamide-derived drugs.

WARNINGS: *General: Enalapril Maleate, Hypotension:* Excessive hypotension was rarely seen in uncomplicated hypertensive patients but is a possible consequence of enalapril use in severely salt/volume depleted persons such as those treated vigorously with diuretics or patients on dialysis.

Syncope has been reported in 1-3 percent of patients receiving VASERETIC. In patients receiving enalapril alone, the incidence of syncope is 0.5 percent. The overall incidence of syncope may be reduced by proper titration of the individual components. (See PRECAUTIONS, *Drug Interactions*, and ADVERSE REACTIONS.)

In patients with severe congestive heart failure, with or without associated renal insufficiency, excessive hypotension has been observed and may be associated with oliguria and/or progressive azotemia, and rarely with acute renal failure and/or death. Because of the potential fall in blood pressure in these patients, therapy should be started under very close medical supervision. Such patients should be followed closely for the first two weeks of treatment and whenever the dose of enalapril and/or diuretic is increased. Similar considerations may apply to patients with ischemic heart or cerebrovascular disease, in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident.

If hypotension occurs, the patient should be placed in the supine position and, if necessary, receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses, which usually can be given without difficulty once the blood pressure has increased after volume expansion.

Angioedema: Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported in patients treated with angiotensin converting enzyme inhibitors, including enalapril. In such cases VASERETIC should be promptly discontinued and appropriate therapy and monitoring should be provided until complete and sustained resolution of signs and symptoms has occurred. In instances where swelling has been confined to the face and lips the condition has generally resolved without treatment, although antihistamines have been useful in relieving symptoms. Angioedema associated with laryngeal edema may be fatal. **Where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, appropriate therapy, e.g., subcutaneous epinephrine solution 1:1000 (0.3 mL to 0.5 mL) and/or measures necessary to ensure a patent airway, should be promptly provided.** (See ADVERSE REACTIONS.)

Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor (see also CONTRAINDICATIONS).

Neutropenia/Agranulocytosis: Another angiotensin converting enzyme inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression, rarely in uncomplicated patients but more frequently in patients with renal impairment especially if they also have a collagen vascular disease. Available data from clinical trials of enalapril are insufficient to show that enalapril does not cause agranulocytosis at similar rates. Marketing experience has revealed several cases of neutropenia or agranulocytosis in which a causal relationship to enalapril cannot be excluded. Periodic monitoring of white blood cell counts in patients with collagen vascular disease and renal disease should be considered.

Hydrochlorothiazide: Thiazides should be used with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. Cumulative effects of the drug may develop in patients with impaired renal function.

Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.

Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma.

The possibility of exacerbation or activation of systemic lupus erythematosus has been reported.

Lithium generally should not be given with thiazides (see PRECAUTIONS, *Drug Interactions, Enalapril Maleate and Hydrochlorothiazide*).

Pregnancy: Enalapril-Hydrochlorothiazide: There was no teratogenicity in rats given up to 90 mg/kg/day of enalapril (150 times the maximum human dose) in combination with 10 mg/kg/day of hydrochlorothiazide (2 1/2 times the maximum human dose) or in mice given up to 30 mg/kg/day of enalapril (50 times the maximum human dose) in combination with 10 mg/kg/day of hydrochlorothiazide (2 1/2 times the maximum human dose). At these doses, fetotoxicity expressed as a decrease in average fetal weight occurred in both species. No fetotoxicity occurred at lower doses, 30/10 mg/kg/day of enalapril-hydrochlorothiazide in rats and 10/10 mg/kg/day of enalapril-hydrochlorothiazide in mice.

When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, VASERETIC should be discontinued as soon as possible. (See *Enalapril Maleate, Fetal/Neonatal Morbidity and Mortality*, below.)

Enalapril Maleate: Fetal/Neonatal Morbidity and Mortality: ACE inhibitors can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature. When pregnancy is detected, ACE inhibitors should be discontinued as soon as possible.

The use of ACE inhibitors during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to the ACE-inhibitor exposure.

These adverse effects do not appear to have resulted from intrauterine ACE-inhibitor exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to ACE inhibitors only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should make every effort to discontinue the use of VASERETIC as soon as possible.

Rarely (probably less often than once in every thousand pregnancies), no alternative to ACE inhibitors will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intrauterine environment.

If oligohydramnios is observed, VASERETIC should be discontinued unless it is considered lifesaving for the mother. Contraction stress testing (CST), a non-stress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of *in utero* exposure to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function. Enalapril, which crosses the placenta, has been removed from neonatal circulation by peritoneal dialysis with some clinical benefit, and theoretically may be removed by exchange transfusion, although there is no experience with the latter procedure.

No teratogenic effects of enalapril were seen in studies of pregnant rats, and rabbits. On a mg/kg basis, the doses used were up to 333 times (in rats), and 50 times (in rabbits) the maximum recommended human dose.

Hydrochlorothiazide: Teratogenic Effects: Reproduction studies in the rabbit, the mouse and the rat at doses up to 100 mg/kg/day (50 times the human dose) showed no evidence of external abnormalities of the fetus due to hydrochlorothiazide. Hydrochlorothiazide given in a two-litter study in rats at doses of 4 - 5.6 mg/kg/day (approximately 1 - 2 times the usual daily human dose) did not impair fertility or produce birth abnormalities in the offspring. Thiazides cross the placental barrier and appear in cord blood.

Nonteratogenic Effects: These may include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult.

PRECAUTIONS: *General: Enalapril Maleate, Impaired Renal Function:* As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe congestive heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with angiotensin converting enzyme inhibitors, including enalapril, may be associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death.

In clinical studies in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine were observed in 20 percent of patients. These increases were almost always reversible upon discontinuation of enalapril and/or diuretic therapy. In such patients renal function should be monitored during the first few weeks of therapy.

Some patients with hypertension or heart failure with no apparent preexisting renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when enalapril has been given concomitantly with a diuretic. This is more likely to occur in patients with pre-existing renal impairment. Dosage reduction of enalapril and/or discontinuation of the diuretic may be required.

Evaluation of the hypertensive patient should always include assessment of renal function.

Hemodialysis Patients: Anaphylactoid reactions have been reported in patients dialyzed with high-flux membranes (e.g., AN 69*) and treated concomitantly with an ACE inhibitor. In these patients consideration should be given to using a different type of dialysis membrane or a different class of antihypertensive agent.

Hyperkalemia: Elevated serum potassium (greater than 5.7 mEq/L) was observed in approximately one percent of hypertensive patients in clinical trials treated with enalapril alone. In most cases these were isolated values which resolved despite continued therapy, although hyperkalemia was a cause of discontinuation of therapy in 0.28 percent of hypertensive patients. Hyperkalemia was less frequent (approximately 0.1 percent) in patients treated with enalapril plus hydrochlorothiazide. Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with enalapril. (See *Drug Interactions*.)

Cough: Cough has been reported with the use of ACE inhibitors. Characteristically, the cough is nonproductive, persistent and resolves after discontinuation of therapy. ACE inhibitor-induced cough should be considered as part of the differential diagnosis of cough.

Surgery/Anesthesia: In patients undergoing major surgery or during anesthesia with agents that produce hypotension, enalapril may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Hydrochlorothiazide: Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals. All patients receiving thiazide therapy should be observed for clinical signs of fluid or electrolyte imbalance: hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Warning signs or symptoms of fluid and electrolyte imbalance, irrespective of cause, include dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, confusion, seizures, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting.

Hypokalemia may develop, especially with brisk diuresis, when severe cirrhosis is present, or after prolonged therapy. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Hypokalemia may cause cardiac arrhythmia and may also sensitize or exaggerate the response of the heart to the toxic effects of digitalis (e.g., increased ventricular irritability). Because enalapril reduces the production of aldosterone, concomitant therapy with enalapril attenuates the diuretic-induced potassium loss (see *Drug Interactions, Agents Increasing Serum Potassium*).

Although any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease), chloride replacement may be required in the treatment of metabolic alkalosis.

Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction, rather than administration of salt except in rare instances when the hyponatremia is life-threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Hyperuricemia may occur or frank gout may be precipitated in certain patients receiving thiazide therapy.

In diabetic patients dosage adjustments of insulin or oral hypoglycemic agents may be required. Hyperglycemia may occur with thiazide diuretics. Thus latent diabetes mellitus may become manifest during thiazide therapy.

The antihypertensive effects of the drug may be enhanced in the postsympathectomy patient.

If progressive renal impairment becomes evident consider withholding or discontinuing diuretic therapy.

Thiazides have been shown to increase the urinary excretion of magnesium; this may result in hypomagnesemia.

Thiazides may decrease urinary calcium excretion. Thiazides may cause intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

Increases in cholesterol and triglyceride levels may be associated with thiazide diuretic therapy.

Information for Patients, Angioedema: Angioedema, including laryngeal edema, may occur especially following the first dose of enalapril. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, extremities, eyes, lips, tongue, difficulty in swallowing or breathing) and to take no more drug until they have consulted with the prescribing physician.

Hypotension: Patients should be cautioned to report lightheadedness especially during the first few days of therapy. If actual syncope occurs, the patients should be told to discontinue the drug until they have consulted with the prescribing physician.

All patients should be cautioned that excessive perspiration and dehydration may lead to an excessive fall in blood pressure because of reduction in fluid volume. Other causes of volume depletion such as vomiting or diarrhea may also lead to a fall in blood pressure; patients should be advised to consult with the physician.

Hyperkalemia: Patients should be told not to use salt substitutes containing potassium without consulting their physician.

Neutropenia: Patients should be told to report promptly any indication of infection (e.g., sore throat, fever) which may be a sign of neutropenia.

Pregnancy: Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to ACE inhibitors, and they should also be told that these consequences do not appear to have resulted from intrauterine ACE-inhibitor exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.

NOTE: As with many other drugs, certain advice to patients being treated with VASERETIC is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Drug Interactions: Enalapril Maleate, Hypotension—Patients on Diuretic Therapy: Patients on diuretics and especially those in whom diuretic therapy was recently instituted, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with enalapril. The possibility of hypotensive effects with enalapril can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with enalapril. If it is necessary to continue the diuretic, provide medical supervision for at least two hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS.)

Agents Causing Renin Release: The antihypertensive effect of enalapril is augmented by antihypertensive agents that cause renin release (e.g., diuretics).

Other Cardiovascular Agents: Enalapril has been used concomitantly with beta adrenergic-blocking agents, methyldopa, nitrates, calcium-blocking agents, hydralazine and prazosin without evidence of clinically significant adverse interactions.

Agents Increasing Serum Potassium: Enalapril attenuates diuretic-induced potassium loss. Potassium-sparing diuretics (e.g., spironolactone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium. Therefore, if concomitant use of these agents is indicated because of demonstrated hypokalemia they should be used with caution and with frequent monitoring of serum potassium.

Lithium: Lithium toxicity has been reported in patients receiving lithium concomitantly with drugs which cause elimination of sodium, including ACE inhibitors. A few cases of lithium toxicity have been reported in patients receiving concomitant enalapril and lithium and were reversible upon discontinuation of both drugs. It is recommended that serum lithium levels be monitored frequently if enalapril is administered concomitantly with lithium.

Hydrochlorothiazide: When administered concurrently the following drugs may interact with thiazide diuretics:

Alcohol, barbiturates, or narcotics—potentiation of orthostatic hypotension may occur.

Antidiabetic drugs (oral agents and insulin)—dosage adjustment of the antidiabetic drug may be required.

Other antihypertensive drugs—additive effect or potentiation.

Cholestyramine and colestipol resins—Cholestyramine and colestipol resins bind the hydrochlorothiazide and reduce its absorption from the gastrointestinal tract by up to 85 and 43 percent, respectively. Thiazides may be administered two to four hours before the resin when the two drugs are used concomitantly.

Corticosteroids, ACTH—intensified electrolyte depletion, particularly hypokalemia.

Pressor amines (e.g., norepinephrine)—possible decreased response to pressor amines but not sufficient to preclude their use.

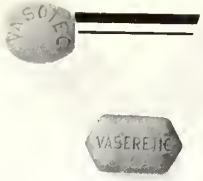
Skeletal muscle relaxants, nondepolarizing (e.g., tubocurarine)—possible increased responsiveness to the muscle relaxant.

Lithium—should not generally be given with diuretics. Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity. Refer to the package insert for lithium preparations before use of such preparations with VASERETIC.

Non-steroidal Anti-inflammatory Drugs—In some patients, the administration of a non-steroidal anti-inflammatory agent can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing and thiazide diuretics. Therefore, when VASERETIC and non-steroidal anti-inflammatory agents are used concomitantly, the patient should be observed closely to determine if the desired effect of the diuretic is obtained.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Enalapril in combination with hydrochlorothiazide was not mutagenic in the Ames microbial mutagen test with or without metabolic activation. Enalapril-hydrochlorothiazide did not produce DNA single strand breaks in an *in vitro* alkaline elution assay in rat hepatocytes or chromosomal aberrations in an *in vivo* mouse

10 mg



25 mg

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bone marrow assay.

Enalapril Maleate: There was no evidence of a tumorigenic effect when enalapril was administered for 106 weeks to rats at doses up to 90 mg/kg/day (150 times* the maximum daily human dose). Enalapril has also been administered for 94 weeks to male and female mice at doses up to 90 and 180 mg/kg/day, respectively, (150 and 300 times* the maximum daily dose for humans) and showed no evidence of carcinogenicity.

Neither enalapril maleate nor the active diacid was mutagenic in the Ames microbial mutagen test with or without metabolic activation. Enalapril was also negative in the following genotoxicity studies: rec-assay, reverse mutation assay with *E. coli*, sister chromatid exchange with cultured mammalian cells, and the micronucleus test with mice, as well as in an *in vivo* cytogenic study using mouse bone marrow.

There were no adverse effects on reproductive performance in male and female rats treated with 10 to 90 mg/kg/day of enalapril.

Hydrochlorothiazide: Two-year feeding studies in mice and rats conducted under the auspices of the National Toxicology Program (NTP) uncovered no evidence of a carcinogenic potential of hydrochlorothiazide in female mice (at doses of up to approximately 600 mg/kg/day) or in male and female rats (at doses of up to approximately 100 mg/kg/day). The NTP, however, found equivocal evidence for hepatocarcinogenicity in male mice.

Hydrochlorothiazide was not genotoxic *in vitro* in the Ames mutagenicity assay of *Salmonella typhimurium* strains TA 98, TA 100, TA 1535, TA 1537, and TA 1538 and in the Chinese Hamster Ovary (CHO) test for chromosomal aberrations, or *in vivo* in assays using mouse germinal cell chromosomes, Chinese hamster bone marrow chromosomes, and the *Drosophila* sex-linked recessive lethal trait gene. Positive test results were obtained only in the *in vitro* CHO Sister Chromatid Exchange (clastogenicity) and in the Mouse Lymphoma Cell (mutagenicity) assays, using concentrations of hydrochlorothiazide from 43 to 1300 μg/ml, and in the *Aspergillus nidulans* non-disjunction assay at an unspecified concentration.

Hydrochlorothiazide had no adverse effects on the fertility of mice and rats of either sex in studies wherein these species were exposed, via their diet, to doses of up to 100 and 4 mg/kg, respectively, prior to conception and throughout gestation.

Pregnancy: Pregnancy Categories C (first trimester) *and D* (second and third trimesters). See WARNINGS, *Pregnancy, Enalapril Maleate, Fetal/Neonatal Morbidity and Mortality.*

Nursing Mothers: Enalapril and enalaprilat are detected in human milk in trace amounts. Thiazides do appear in human milk. Because of the potential for serious reactions in nursing infants from either drug, a decision should be made whether to discontinue nursing or to discontinue VASERETIC, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: VASERETIC has been evaluated for safety in more than 1500 patients, including over 300 patients treated for one year or more. In clinical trials with VASERETIC no adverse experiences peculiar to this combination drug have been observed. Adverse experiences that have occurred, have been limited to those that have been previously reported with enalapril or hydrochlorothiazide.

The most frequent clinical adverse experiences in controlled trials were: dizziness (8.6 percent), headache (5.5 percent), fatigue (3.9 percent) and cough (3.5 percent). Adverse experiences occurring in greater than two percent of patients treated with VASERETIC in controlled clinical trials were: muscle cramps (2.7 percent), nausea (2.5 percent), asthenia (2.4 percent), orthostatic effects (2.3 percent), impotence (2.2 percent), and diarrhea (2.1 percent).

Clinical adverse experiences occurring in 0.5 to 2.0 percent of patients in controlled trials included: *Body As A Whole:* Syncope, chest pain, abdominal pain, *Cardiovascular:* Orthostatic hypotension, palpitation, tachycardia, *Digestive:* Vomiting, dyspepsia, constipation, flatulence, dry mouth, *Nervous/Psychiatric:* Insomnia, nervousness, paresthesia, somnolence, vertigo; *Skin:* Pruritus, rash, *Other:* Dyspnea, gout, back pain, arthralgia, diaphoresis, decreased libido, tinnitus, urinary tract infection.

Angioedema: Angioedema has been reported in patients receiving VASERETIC (0.6 percent). Angioedema associated with laryngeal edema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis and/or larynx occurs, treatment with VASERETIC should be discontinued and appropriate therapy instituted immediately. (See WARNINGS.)

Hypotension: In clinical trials, adverse effects relating to hypotension occurred as follows: hypotension (0.9 percent), orthostatic hypotension (1.5 percent), other orthostatic effects (2.3 percent). In addition syncope occurred in 1.3 percent of patients. (See WARNINGS.)

Cough: See PRECAUTIONS, *Cough.*

Clinical Laboratory Test Findings, Serum Electrolytes: See PRECAUTIONS.

Creatinine, Blood Urea Nitrogen: In controlled clinical trials minor increases in blood urea nitrogen and serum creatinine, reversible upon discontinuation of therapy, were observed in about 0.6 percent of patients with essential hypertension treated with VASERETIC. More marked increases have been reported in other enalapril experience. Increases are more likely to occur in patients with renal artery stenosis. (See PRECAUTIONS.)

Serum Uric Acid, Glucose, Magnesium, and Calcium: See PRECAUTIONS.

Hemoglobin and Hematocrit: Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.3 g percent and 1.0 vol percent, respectively) occur frequently in hypertensive patients treated with VASERETIC but are rarely of clinical importance unless another cause of anemia coexists. In clinical trials, less than 0.1 percent of patients discontinued therapy due to anemia.

Liver Function Tests: Rarely, elevations of liver enzymes and/or serum bilirubin have occurred.

Other adverse reactions that have been reported with the individual components are listed below and, within each category, are in order of decreasing severity.

Enalapril Maleate—Enalapril has been evaluated for safety in more than 10,000 patients. In clinical trials adverse reactions which occurred with enalapril were also seen with VASERETIC. However, since enalapril has been marketed, the following adverse reactions have been reported: *Body As A Whole:* Anaphylactoid reactions (see PRECAUTIONS, *Hemodialysis Patients*), *Cardiovascular:* Cardiac arrest, myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high risk patients (see WARNINGS, *Hypotension*); pulmonary embolism and infarction, pulmonary edema; rhythm disturbances including atrial tachycardia and bradycardia; atrial fibrillation, hypotension, angina pectoris, *Digestive:* Ileus, pancreatitis, hepatic failure, hepatitis (hepatocellular [proven on rechallenge] or cholestatic jaundice), melena, anorexia, glossitis, stomatitis, dry mouth, *Hematologic:* Rare cases of neutropenia, thrombocytopenia and bone marrow depression, a few cases of hemolysis in patients with G-6-PD deficiency have been reported in which a causal relationship to enalapril cannot be excluded, *Nervous System/Psychiatric:* Depression, confusion, ataxia, peripheral neuropathy (e.g., paresthesia, dysesthesia), *Urogenital:* Renal failure, oliguria, renal dysfunction (see PRECAUTIONS), flank pain, gynecomastia; *Respiratory:* Pulmonary infiltrates, bronchospasm, pneumonia, bronchitis, rhinorrhea, sore throat and hoarseness, asthma, upper respiratory infection; *Skin:* Exfoliative dermatitis, toxic epidermal necrolysis, Stevens-Johnson syndrome, herpes zoster, erythema multiforme, urticaria, alopecia, flushing, photosensitivity, *Special Senses:* Blurred vision, taste alteration, anosmia, conjunctivitis, dry eyes, tearing.

Miscellaneous: A symptom complex has been reported which may include a positive ANA, an elevated erythrocyte sedimentation rate, arthralgia/arthritis, myalgia, fever, serositis, vasculitis, leukocytosis, eosinophilia, photosensitivity, rash and other dermatologic manifestations.

Fetal/Neonatal Morbidity and Mortality: See WARNINGS, *Pregnancy, Enalapril Maleate, Fetal/Neonatal Morbidity and Mortality.*

Hydrochlorothiazide—Body as a Whole: Weakness, *Digestive:* Pancreatitis, jaundice (intrahepatic cholestatic jaundice), sialadenitis, cramping, gastric irritation, anorexia; *Hematologic:* Aplastic anemia, agranulocytosis, leukopenia, hemolytic anemia, thrombocytopenia, *Hypersensitivity:* Purpura, photosensitivity, urticaria, necrotizing angiitis (vasculitis and cutaneous vasculitis), fever, respiratory distress including pneumonitis and pulmonary edema, anaphylactic reactions, *Musculoskeletal:* Muscle spasm; *Nervous System/Psychiatric:* Restlessness, *Renal:* Renal failure, renal dysfunction, interstitial nephritis (see WARNINGS); *Skin:* Erythema multiforme including Stevens-Johnson syndrome, exfoliative dermatitis including toxic epidermal necrolysis, alopecia, *Special Senses:* Transient blurred vision, xanthopsia.

* Based on patient weight of 50 kg.

For more detailed information, consult your DuPont Pharma Representative or see Prescribing Information.

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In Memoriam

California Medical Association

Batterman, Robert C., Berkeley. Died Jun 11, 1993, aged 60. Graduate of New York University School of Medicine, New York, 1935. Licensed in California in 1959. Dr Batterman was a member of the Alameda-Contra Costa Medical Association.

Binckley, John W., Eureka. Died Aug 18, 1993, aged 80. Graduate of University of Rochester School of Medicine and Dentistry, Rochester, New York. Licensed in California in 1946. Dr Binckley was a member of the Humboldt-Del Norte Medical Society.

Black, Lawrence C., Fresno. Died Aug 10, 1993, aged 71. Graduate of University of California Irvine-California College of Medicine, 1962. Licensed in California in 1975. Dr Black was a member of the Fresno-Madera Medical Society.

Black, William A., Sacramento. Died Aug 9, 1993, aged 93. Graduate of Washington University School of Medicine, St Louis, Missouri, 1942. Licensed in California in 1943. Dr Black was a member of the Sacramento-El Dorado Medical Society.

Block, Robert Elliot, Stockton. Died Sep 28, 1993, aged 78. Graduate of Boston University School of Medicine, Boston, Massachusetts, 1940. Licensed in California in 1975. Dr Block was a member of the San Joaquin County Medical Society.

Brewster, Henry H., Stockton. Died Sep 15, 1993, aged 80. Graduate of Harvard Medical School, 1938. Licensed in California in 1965. Dr Brewster was a member of the San Joaquin County Medical Society.

Cantrell, Glenn, Modesto. Died August 1993, aged 72. Graduate of University of Southern California, Los Angeles, 1947. Licensed in California in 1947. Dr Cantrell was a member of the Stanislaus Medical Society.

Chin, Edward J. H., Oakland. Died May 29, 1993, aged 62. Graduate of McGill University Faculty of Medicine, Montreal, 1959. Licensed in California in 1962. Dr Chin was a member of the Alameda-Contra Costa Medical Association.

Conley, Edward H., Modesto. Died Oct 13, 1993, aged 49. Graduate of Johns Hopkins University School of Medicine, Baltimore, Maryland, 1969. Licensed in California in 1971. Dr Conley was a member of the Stanislaus Medical Society.

Ekroth, Richard D., Loma Linda. Died Aug 21, 1993, aged 77. Graduate of Loma Linda University School of Medicine, 1943. Licensed in California in 1944. Dr Ekroth was a member of the San Bernardino County Medical Society.

Engelhardt, Jack E., Corona del Mar. Died Aug 18, 1993, aged 71. Graduate of Medical College of Wisconsin, Milwaukee, 1946. Licensed in California in 1947. Dr Engelhardt was a member of the Orange County Medical Association.

Goble, Garvin G., Fortuna. Died Sep 12, 1993, aged 77. Graduate of Jefferson Medical College, Philadelphia, Pennsylvania, 1942. Licensed in California in 1942. Dr Goble was a member of the Humboldt-Del Norte Medical Society.

Greenberg, Jacob, San Jose. Died Oct 20, 1993, aged 86. Graduate of Yale University School of Medicine, New Haven, Connecticut, 1933. Licensed in California in 1943. Dr Greenberg was a member of the Santa Clara County Medical Association.

Harmeling, James G., Redlands. Died Jul 24, 1993, aged 62. Graduate of Creighton University School of Medicine, Omaha, Nebraska, 1957. Licensed in California in 1967. Dr Harmeling was a member of the San Bernardino County Medical Society.

Heald, John H., San Francisco. Died Aug 1, 1993, aged 70. Graduate of Stanford University School of Medicine, Stanford, California, 1948. Licensed in California in 1948. Dr Heald was a member of the San Francisco Medical Society.

Higgins, James H., San Diego. Died Aug 1993, aged 83. Graduate of Wayne State University School of Medicine, Detroit, Michigan, 1940. Licensed in California in 1946. Dr Higgins was a member of the San Diego County Medical Society.

Hudson, John W., Sacramento. Died Aug 17, 1993, aged 59. Graduate of Howard University School of Medicine, Washington, DC, 1959. Licensed in California in 1963. Dr Hudson was a member of the Sacramento-El Dorado Medical Society.

Inghram, Howard D., San Bernardino. Died Sep 19, 1993, aged 94. Graduate of Northwestern University Medical School, Chicago, Illinois, 1927. Licensed in California in 1927. Dr Inghram was a member of the San Bernardino County Medical Society.

Leask, William H., Bakersfield. Died Aug 5, 1993, aged 77. Graduate of University of Nebraska College of Medicine, Omaha, 1948. Licensed in California in 1949. Dr Leask was a member of the Kern County Medical Society.

Leopold, Irving H., Irvine. Died Aug 2, 1993, aged 78. Graduate of University of Pennsylvania School of Medicine, Philadelphia, 1938. Licensed in California in 1974. Dr Leopold was a member of the Orange County Medical Association.

Mitchell, Stephen P., Fremont. Died Mar 24, 1993, aged 50. Graduate of University of California, Los Angeles, School of Medicine, 1972. Licensed in California in 1973. Dr Mitchell was a member of the Alameda-Contra Costa Medical Association.

Moyce, Robert W., San Bernardino. Died Aug 3, 1993, aged 77. Graduate of State University of New York at Buffalo Medical School, 1943. Licensed in California in 1954. Dr Moyce was a member of the San Bernardino County Medical Society.

Murray, Arthur J., Fairfield. Died Aug 18, 1993, aged 54. Graduate of Howard University School of Medicine, Washington, DC, 1965. Licensed in California in 1966. Dr Murray was a member of the Solano County Medical Society.

Nielsen, Lester R., Fresno. Died Aug 21, 1993, aged 93. Graduate of University of Louisville School of Medicine, Louisville, Kentucky, 1927. Licensed in California in 1928. Dr Nielsen was a member of the Fresno-Madera Medical Society.

Olney, Mary B., San Francisco. Died Aug 25, 1993, aged 85. Graduate of University of California, San Francisco, School of Medicine, 1932. Licensed in California in 1933. Dr Olney was a member of the San Francisco Medical Society.

Pitchford, Clyde A., Jr, Riverside. Died Jul 12, 1993, aged 72. Graduate of Stanford University School of Medicine, Stanford, California, 1945. Licensed in California in 1945. Dr Pitchford was a member of the Riverside County Medical Association.

Plumb, Robert T., Coronado. Died Jul 16, 1993, aged 77. Graduate of University of Michigan Medical School, Ann Arbor, 1940. Licensed in California in 1944. Dr Plumb was a member of the San Diego County Medical Society.

Redding, Marion D., San Diego. Died Aug 1993, aged 83. Graduate of Tulane University School of Medicine, New Orleans, Louisiana, 1934. Licensed in California in 1941. Dr Redding was a member of the San Diego County Medical Society.

Roach, Paul A., Santa Cruz. Died Sep 6, 1993, aged 77. Graduate of Stanford University School of Medicine, Stanford, California, 1943. Licensed in California in 1943. Dr Roach was a member of the Santa Cruz County Medical Society.

Sanders, Michael Ennis, Los Gatos. Died Sep 23, 1993, aged 49. Graduate of University of Maryland School of Medicine, Baltimore, 1971. Licensed in California in 1976. Dr Sanders was a member of the Santa Clara County Medical Association.

(Continued on Page 725)

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PROGRAM PROFILE

Center For Skull Base Surgery

A CASE STUDY

A 35-year-old man presented with the acute onset of a severe headache. Diagnostic tests revealed an intracranial aneurysm at the junction of the basilar artery and the anterior inferior cerebellar artery, causing sub-arachnoid hemorrhage. Operative approaches for aneurysms in that area are considered difficult and dangerous.

Nevertheless, surgeons at the Center for Skull Base Surgery used a new technique, combining an approach through the temporal bone with newer microsurgical instrumentation.

The otolaryngologist, Dr. Dennis R. Maceri, first drilled out the mastoid, identifying those structures related to hearing that were to be preserved. Dr. Steven L. Giannotta, neurosurgeon, then dissected the aneurysm and put clips on it to obliterate it. Dr. Maceri finished the procedure by closing the brain covering with a watertight fat graft from the patient's lower abdomen.

The patient has made a full recovery and resumed his normal activities of weight lifting, skiing and flying ultra light aircraft.

Historically, lesions at the base of the skull have represented some of the most difficult challenges in operative neurosurgery. Older techniques at management of tumors or vascular lesions in this region were not satisfactory. The cavernous sinus, in particular, represented a "no man's land" because of the risks associated with direct surgical intervention in this area.

However, recent advances in diagnostic imaging and surgical techniques have allowed direct operative management of skull base lesions to become a reality. The advent of magnetic resonance imaging, sophisticated angiography and a better understanding of surgical micro-anatomy in conjunction with improvements in microsurgical instrumentation have enabled previous "inoperable" lesions to now be excised with acceptable risks.

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The highly sensitive intracranial area requires the extensive skill and collaborative approach that can only be provided by several specialties, working in harmony. In 1990, USC University Hospital organized a specialized team of internationally renowned surgeons in the fields of neurosurgery, plastic and reconstructive surgery, otolaryngology, neuroanesthesia, neuropathology, neurointerventional radiology and neuro-ophthalmology to work together as a closely coordinated team. The integration of this wide range of experts allows the USC University Hospital Center for Skull Base Surgery to offer a comprehensive, multi-specialty program to manage complicated skull base lesions. The Center for Skull Base Surgery incorporates the talents of these disciplines under the leadership of Director Takanori Fukushima, M.D., D.M.Sc., an internationally recognized pioneer in skull base surgery and Associate Director William T. Couldwell, M.D., Ph.D., a specialist in brain tumors and tumor biology research.

The USC University Hospital Center for Skull Base Surgery, one of the most comprehensive programs of its kind in the United States, serves as a primary West Coast referral center for intracranial disorders. Members of the interdisciplinary team are committed to maintaining close contact with referring physicians to ensure effective patient management for optimal recovery.

SKULL BASE SURGERY TEAM
Takanori Fukushima, M.D., D.M.Sc., Director
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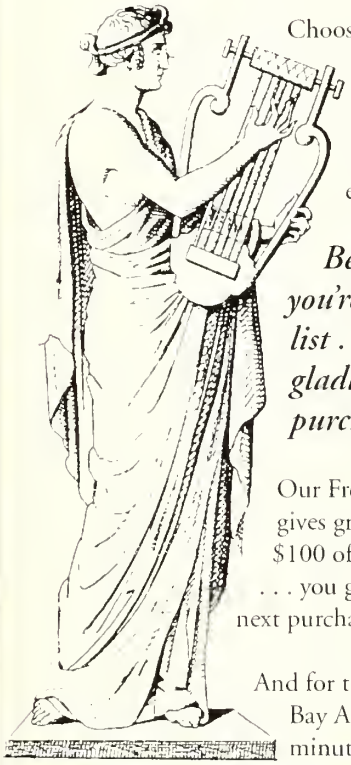

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References:

1. A. Morales et al., New England Journal of Medicine: 1221. November 12, 1981.
2. Goodman, Gilman — The Pharmacological basis of Therapeutics 6th ed., p. 176-188. McMillan December Rev. 1/85.
3. Weekly Urological Clinical Letter, 27:2, July 4, 1983.
4. A. Morales et al., The Journal of Urology 128: 45-47, 1982.

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Brochures and registration forms are available from the contact person or organization sponsoring the program.

June 2-4—**Arizona Medical Association Annual Meeting**. Scottsdale Plaza Resort. Thurs-Sat. Contact: ArMA.

CONTACT INFORMATION

ArMA—Contact: Arizona Medical Association, 810 W Bethany Home Rd, Phoenix, AZ 85013. (602) 246-8901.
Mayo Clinic-Scottsdale— Contact: Postgraduate Courses, Mayo Clinic-Scottsdale, (602) 301-7447.
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ALLERGY/IMMUNOLOGY

January 23-27—**Western Society of Allergy and Immunology: 32nd Annual Scientific Session.** Western Society of Allergy and Immunology at Ritz-Carlton, Mauna Lani, Island of Hawaii. Sun-Thurs. Contact: Rebecca Smith, PO Box 82268, Portland, OR 97282. (503) 774-3105.

February 3-5—**Immunology and the Clinical Practice of Allergy.** UCSD at San Diego. Thurs-Sat. 20 hrs. $285. Contact: UCSD.

March 19—**Immunologic Controversies Facing the Private Practitioner.** California Medical Association's Western Scientific Assembly at Disneyland Hotel, Anaheim. Sat. 3.5 hrs. Contact: Arlene Sirott, (415) 882-3384.

ANESTHESIOLOGY

January 5-8—**Anesthesia Update 1994.** UCSD at Hotel del Coronado, San Diego. Wed-Sat. 21 hrs. $350. Contact: UCSD.

January 16-22—**Hawaiian Seminar on Clinical Anesthesia.** California Society of Anesthesiologists at Westin Maui, Kaanapali Beach. Sun-Sat. 21 hrs. $425. Contact: CSA, 1065 E Hillsdale Blvd, Ste 410, Foster City 94404. (800) 345-3691.

January 28-30—**32nd Clinical Conference in Pediatric Anesthesiology.** Children's Hospital Los Angeles at Disneyland Hotel, Anaheim. Fri-Sun. 15 hrs. Contact: Children's Hospital, PO Box 54700, Los Angeles 90054. (213) 669-2262.

February 23-27—**The Practicing Physician's Approach to the Difficult Headache Patient.** Dannemiller Memorial Educational Foundation at Marriott's Rancho Las Palmas Resort and Country Club, Rancho Mirage. Wed-Sun. Contact: Seymour Diamond, 5252 N Western Ave, Chicago, IL 60625. (312) 907-6226.

March 19-20—**Case Conference in Anesthesia.** California Society of Anesthesiologists at Dana Point Resort. Sat-Sun. 9 hrs. $185. Contact: CSA, 1065 E Hillsdale Blvd, Ste 410, Foster City 94404. (800) 345-3691.

April 2-3—**22nd Obstetric/Anesthesia Conference.** Ohio State Department of Anesthesiology at Sheraton Waikiki Hotel, Honolulu, Hawaii. Sat-Sun. 20 hrs. $610. Contact: Arlene Rogers, 410 W 10th Ave, Columbus, OH 43210. (614) 293-8487.

April 5-8—**Hawaiian Pain Conference.** Ohio State University Department of Anesthesiology at Grand Hyatt, Wailea, Maui. Tues-Fri. 16 hrs. $610. Contact: Arlene Rogers, Ohio State University, 410 W 10th Ave, Columbus, OH 43210. (614) 293-8153.

April 9-10—**39th PGA Conference.** Los Angeles County Society of Anesthesiologists at UCLA Faculty Center. Sat-Sun. 13 hrs. Contact: LACSA, PO Box 90999, Long Beach 90809-0999. (213) 597-2661.

May 19-22—**California Society of Anesthesiologists Annual Meeting.** California Society of Anesthesiologists at Monterey Conference Center. Thurs-Sun. 20 hrs. $225-$325. Contact: CSA, 1065 E Hillsdale Blvd, Ste 410, Foster City 94404. (800) 345-3691.

CARDIOLOGY

January 28-29—**Coronary Heart Disease.** American College of Emergency Physicians at Las Vegas Hilton, Nevada. Fri-Sat. 11 hrs. Contact: Karen Debont, Medical Education Resources, 1500 W Canal Ct, Ste 500, Littleton, CO 80120-4528. (800) 421-3756.

February 25-26—**Arrhythmias: Interpretation, Diagnosis, and Management.** American College of Emergency Physicians at Desert Inn, Las Vegas, Nevada. Fri-Sat. 11 hrs. Contact: Karen Debont, Medical Education Resources, 1500 W Canal Ct, Ste 500, Littleton, CO 80120-4528. (800) 421-3756.

February 26—**Cardiology for the Primary Care Physician.** UCD at Cancer Center Auditorium, Sacramento. Sat. 7 hrs. $95. Contact: UCD.

February 26-March 5—**Cardiovascular Emergencies.** UCSD at Lahaina, Maui, Hawaii. 1 week. 21 hrs. $450. Contact: Edith Bookstein, (619) 454-3212.

March 25-26—**Cardiac Diagnostic Methods and Risk Management.** American College of Emergency Physicians at MGM Grand, Las Vegas, Nevada. Fri-Sat. 11 hrs. Contact: Karen Debont, Medical Education Resources, 1500 W Canal Ct, Ste 500, Littleton, CO 80120-4528. (800) 421-3756.

April 11-13—**4th Annual Symposium on Coronary Stenting.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Mon-Wed. 20 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

May 13-15—**Arrhythmias: Interpretation, Diagnosis, and Management.** American College of Emergency Physicians at Doubletree Resort, Palm Springs. Fri-Sun. 11 hrs. Contact: Karen Debont, Medical Education Resources, 1500 W Canal Ct, Ste 500, Littleton, CO 80120-4528. (800) 421-3756.

DERMATOLOGY

January 21-23—**Cutaneous Malignancies: 1994 Skin Cancer Update.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Fri-Sun. 17 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

January 21-23—**Practical Dermatology and Dermatologic Office Procedures for the Primary Care Physician.** UCSD at Hyatt Regency, La Jolla. Fri-Sun. 20 hrs. $495. Contact: Jacqueline Shiller, (619) 223-2997.

March 18—**Current Issues in Dermatology.** California Medical Association's Western Scientific Assembly at Disneyland Hotel, Anaheim. Fri. 3 hrs. Contact: Arlene Sirott, (415) 882-3384.

EMERGENCY MEDICINE

January 10-14—**Emergency Medicine Symposia I.** UCSD at La Jolla Marriott. Mon-Fri. 32 hrs. $495. Contact: UCSD.

January 19-22—**The California Trauma Conference.** UCSF at San Francisco. Wed-Sat. Contact: UCSF.

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   January 27-29, 1994 Breckenridge, CO

FEBRUARY 1994

5. Renal & Liver Transplantation 1994: Current Issues in Management
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6. 9th Annual Rocky Mountain HIV Disease Conference
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7. Horizons in Surgery
   February 26-March 3, 1994 Breckenridge, CO
8. Colorado Review of Anesthesia
   February 26-March 4, 1994 Vail, CO

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9. Colorado Conference on Decision-Based Family Practice
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17. 18th Annual Dynamic Psychotherapy Program
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19. 19th Annual Primary Musculoskeletal Care Program
    August 7-12, 1994 Breckenridge, CO
20. 4th Annual Musculoskeletal Infection Meeting
    August 17-20, 1994 Snowmass Village, CO

SEPTEMBER 1994

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    September 16-18, 1994 Durango, CO

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January 22-29—**Update: Controversies in Emergency and Primary Care.** UCSD at The Royal Waikoloan, Kohala Coast, Hawaii. 1 wk. Contact: Edith Bookstein, PO Box 2586, La Jolla 92038. (619) 454-3212.

February 20-25—**Emergency Medicine 1994: 17th Annual UCD Winter Conference.** UCD at Hyatt Regency Lake Tahoe, Incline Village, Nevada. Sun-Fri. 25 hrs. $495. Contact: UCD.

February 26-March 5—**Cardiac Emergencies.** UCSD at Royal Lahaina Resort, Maui, Hawaii. 1 wk. 21 hrs. $450. Contact: Edith Bookstein, PO Box 2586, La Jolla 92038. (619) 454-3212.

March 6-11—**14th Annual Mammoth Mountain Emergency Medicine Ski Conference.** American College of Emergency Physicians at Mammoth Lakes. Sun-Fri. 18 hrs. $395. Contact: Daniel Abbott, PO Box 52-B, Newport Beach 92662. (714) 650-4156.

FAMILY PRACTICE/PRIMARY CARE

January 21-23—**Practical Dermatology and Dermatologic Office Procedures for the Primary Care Physician.** UCSD at Hyatt Regency, La Jolla. Fri-Sun. 20 hrs. $495. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

February 1-4—**HIV/AIDS and the Primary Care Practitioner—You Can Make a Difference.** UCD at Hyatt Regency Lake Tahoe, Incline Village, Nevada. Tues-Fri. 15 hrs. $365. Contact: UCD.

February 4-5—**Pediatric Dermatology for the Primary Care Physician.** UCSF and Stanford at Sheraton Palace Hotel, San Francisco. Fri-Sat. 10.5 hrs. $275. Contact: UCSF.

February 5-12—**5th Kaiser Permanente National Conference on Musculoskeletal Medicine.** Kaiser Permanente at Hyatt Regency, Kauai, Hawaii. 1 week. 29 hrs. $400. Contact: Ferdy Massimino, MD, 200 Muir Rd, Martinez 94553. (510) 372-1457.

February 18-20—**Office Gynecology for the Primary Care Physician.** SDSU at Hyatt Islandia, San Diego. Fri-Sun. 20 hrs. $450. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

February 18-21—**46th Scientific Assembly.** California Academy of Family Physicians at Doubletree/Marriott Hotels, Monterey. Fri-Mon. 28 hrs. $235. Contact: Christine Macpherson, (415) 394-9121.

KEY TO ABBREVIATIONS

CMA California Medical Association
Contact: Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690. (415) 541-0900.

CPMC: California Pacific Medical Center
Contact: Continuing Education, California Pacific Medical Center, PO Box 7999, San Francisco 94120. (415) 923-3441.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Herbert M. Thomas, MD, MPH, Director of CME, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th St, Los Angeles 90059. (213) 603-3183.

LLU: Loma Linda University
Contact: Patty Wright, Manager of CME Programs. (909) 824-4963.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Medical School Office Building, Suite X-365, Stanford 94305-6114 (415) 723-5594

UCD: University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, 2701 Stockton Blvd, Sacramento 95817. (916) 734-5390.

UCI: University of California, Irvine
Contact: Melvin I. Marks, MD, Director, Memorial/UCI Center for Health Education, Long Beach Memorial Medical Center, 2801 Atlantic Ave, PO Box 1428, Long Beach, California 90801-1428. (213) 595-3811

UCLA University of California, Los Angeles Extension
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, PO Box 24902, UCLA, Los Angeles 90024 (310) 825-8423.

UCSD University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (619) 534-3940.

UCSF University of California, San Francisco
Contact: Janet Johnson, Administrative Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143 (415) 476-4251.

USC University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 1975 Zonal Ave, KAM314, Los Angeles 90033. (800) 872-1119.

March 18—**Cancer Detection and Follow-Up for the Primary Care Physician.** California Medical Association's Western Scientific Assembly at Disneyland Hotel, Anaheim. Fri. 4 hrs. Contact: Arlene Sirott, (415) 882-3384.

March 19—**Emergencies in Primary Care.** California Medical Association's Western Scientific Assembly at Disneyland Hotel, Anaheim. Sat. 4 hrs. Contact: Arlene Sirott, (415) 882-3384.

March 19—**Psychiatric Emergencies in Primary Care: A How To Primer.** California Medical Association's Western Scientific Assembly at Disneyland Hotel, Anaheim. Sat. 3.5 hrs. Contact: Arlene Sirott, (415) 882-3384.

March 20—**Outpatient Procedures for the Primary Care Physician.** California Medical Association's Western Scientific Assembly at Disneyland Hotel, Anaheim. Sun. 3.5 hrs. Contact: Arlene Sirott, (415) 882-3384.

March 20—**Urology for the Primary Care Physician.** California Medical Association's Western Scientific Assembly at Disneyland Hotel, Anaheim. Sat. 5.5 hrs. Contact: Arlene Sirott, (415) 882-3384.

March 23-25—**Annual Review in Family Medicine: Controversies and Challenges in Primary Care.** UCSF at Hotel Nikko, San Francisco. Wed-Fri. 16 hrs. $300. Contact: UCSF.

March 28-31—**Primary Care in Paradise.** Scripps Clinic and Research Foundation at Princeville Resort, Island of Kauai, Hawaii. Mon-Thurs. 16 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Blvd, La Jolla 92037. (619) 554-8556.

April 21-24—**Office Orthopedics and Bone Radiology for the Primary Care Physician.** Sharp Memorial Hospital at San Diego Princess Resort. Thurs-Sun. 20 hrs. $495. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

May 5-7—**Primary Care for the '90s.** University of Nevada School of Medicine at Resort at Squaw Creek, Olympic Valley. Thurs-Sat. 15.5 hrs. $260-$290. Contact: University of Nevada, Manville Bldg/342, Reno, NV 89557. (702) 784-4605.

May 11-14—**16th Semi-Annual Wound Management for Primary Care Health Professionals.** UCSD at San Diego Hilton Beach and Tennis Resort. Wed-Sat. 17 hrs. $250-$475. Contact: Edith Bookstein, PO Box 2586, La Jolla 92038. (619) 454-3212.

1993-1994—**HIV Primary Care Mini-Residency.** UCSD at Owen Clinic, San Diego. Ongoing. 30 hrs. Contact: UCSD.

GERIATRICS

January 18-22—**11th Annual Intensive Course in Geriatric Medicine and Board Review.** UCLA at Beverly Hilton Hotel, Beverly Hills. Tues-Sat. 44 hrs. $675. Contact: UCLA.

January 28-30—**Breakthroughs in Geriatric Psychiatry.** UCSD at Hotel del Coronado, San Diego. Fri-Sun. 17 hrs. $375. Contact: UCSD.

March 17-18—**Alzheimer's Disease Conference.** Advances in Treatment 1994. UCSD at Pan Pacific Hotel, San Diego. Thurs-Fri. 16 hrs. $195. Contact: UCSD.

March 20—**Long Term Care Update.** California Medical Association's Western Scientific Assembly at Disneyland Hotel, Anaheim. Sun. 3.5 hrs. Contact: Arlene Sirott, (415) 882-3384.

1993-1994—**Mini-residency in Geriatrics.** UCSD at Multi Purpose Facility, San Diego. Ongoing. 40-80 hrs. $195. Contact: UCSD.

1993-1994—**The GGG/Alzheimer's Family Center: Sharing the Caring—Training Series on Dementia.** UCSD. Ongoing. 4 hrs. $25. Contact: UCSD.

INFECTIOUS DISEASES

February 4-5—**12th Annual Infectious Disease Conference.** UCD at Hilton Hotel, Sacramento. Fri-Sat. 11 hrs. $160. Contact: UCD.

INTERNAL MEDICINE

January 19-22—**Advanced Nephrology: Nephrology for the Consultant.** UCSD at Hyatt Islandia Hotel, San Diego. Wed-Sat. 25 hrs. $500. Contact: UCSD.

January 22—**Current Concepts in Hemostasis and Thrombosis.** UCD at Cancer Center Auditorium, Sacramento. Sat. 5 hrs. $25. Contact: UCD.

February 3-5—**17th Annual Neurology for the Non-Neurologists.** UCSD at Pan Pacific Hotel, San Diego. Thurs-Sat. 21 hrs. $450. Contact: Edith Bookstein, PO Box 2586, La Jolla 92038. (619) 454-3212.

February 5—**New Advances in Inflammatory Bowel Disease.** Scripps Clinic and Research Foundation at Green Hospital Amphitheater. Sat. 7 hrs. $140. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

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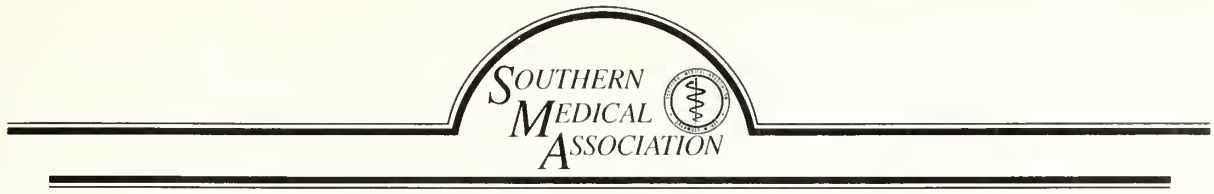

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MARCH 10-12, 1994

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Articles

Prognosis of Mechanically Ventilated Patients

MAXINE A. PAPADAKIS, MD, *San Francisco;* KELVIN K. LEE, PhD, *Palo Alto;*
WARREN S. BROWNER, MD, MPH, *San Francisco, California;* DANIEL L. KENT, MD, *Seattle, Washington;*
DAVID B. MATCHAR, MD, *Durham, North Carolina;* MARGARET K. KAGAWA, MS, *San Francisco;*
JAMES HALLENBECK, MD, *Stanford, California;* DAVID LEE, MD, *Rochester, New York;*
ROBIN ONISHI, MD, *Irvine; and* GERALD CHARLES, MD, *San Francisco, California*

Presented, in part, at the Society of General Internal Medicine national meetings, May 1990 and 1991.

In this Department of Veterans Affairs cooperative study, we examined predictors of in-hospital and 1-year mortality of 612 mechanically ventilated patients from 6 medical intensive care units in a retrospective cohort design. The outcome variable was vital status at hospital discharge and after 1 year. The results showed that 97% of patients were men, the mean age was 63 ± 11 years (SD), and hospital mortality was 64% (95% confidence interval, 60% to 68%). Within the next year, an additional 38% of hospital survivors died, for a total 1-year mortality of 77% (95% confidence interval, 73% to 80%). Hospital and 1-year mortality, respectively, for patients older than 70 years was 76% and 94%, for those with serum albumin levels below 20 grams per liter it was 92% and 96%, for those with an Acute Physiology and Chronic Health Evaluation II (APACHE II) score greater than 35 it was 91% and 98%, and for patients who were being mechanically ventilated after cardiopulmonary resuscitation it was 86% and 90%. The mortality ratio (actual mortality versus APACHE II-predicted mortality) was 1.15. Conclusions are that patient age, APACHE II score, serum albumin levels, or the use of cardiopulmonary resuscitation may identify a subset of mechanically ventilated veterans for whom mechanical ventilation provides little or no benefit.

(Papadakis MA, Lee KK, Browner WS, et al: Prognosis of mechanically ventilated patients. West J Med 1993; 159:659-664)

Determining the prognosis of a patient who receives mechanical ventilation is essential to physicians, patients, and families who are trying to make informed decisions about the appropriateness of life-sustaining therapy. About 20% of patients in medical intensive care units (ICUs) receive mechanical ventilation,[1] the highest level of ICU support.

Previous outcome studies of medical patients treated with mechanical ventilation have been done primarily in university and community hospitals and have noted mortality rates between 50% and 60%.[2,3]* It is uncertain whether these results would apply to hospitals operated by the Department of Veterans Affairs (VA), the single largest health care system in the country and where more than a third of physicians in residency training receive their education.[4]

*See also the editorial by W. A. Knaus, MD, "Predicting Outcome From Mechanical Ventilation," on pages 700-702.

Our previous work suggested that it was possible to identify factors associated with poor survival in veterans who are being mechanically ventilated.[5] These included low serum albumin levels, a high fractional inspired oxygen (Fio_2) concentration after 24 hours on the ventilator, and a high score on the Acute Physiology and Chronic Health Evaluation II (APACHE II) scoring system for severity of illness of patients in ICUs. We undertook this cooperative study to validate these findings and to examine the performance of APACHE II in VA medical centers.

Patients and Methods

Setting and Patients

We did a retrospective cohort study at six VA medical centers: Durham, North Carolina; San Antonio, Texas; Seattle, Washington; West Haven, Connecticut; Long Beach, California; and Palo Alto, California. All six centers are major teaching hospitals of affiliated university

From the Departments of Medicine (Drs Papadakis, Browner, Kagawa, and Charles) and Epidemiology and Biostatistics (Drs Papadakis and Browner), University of California, San Francisco, School of Medicine; the Palo Alto Cooperative Study Program Coordinating Center (Dr K. Lee); the Department of Veterans Affairs Medical Center and Department of Medicine, University of Washington School of Medicine, Seattle (Dr Kent); the Department of Veterans Affairs Medical Center and Department of Medicine, Duke University School of Medicine, Durham, North Carolina (Dr Matchar); the Department of Veterans Affairs Medical Center, Palo Alto, and Department of Medicine, Stanford University School of Medicine, Stanford, California (Dr Hallenbeck); the Department of Veterans Affairs Medical Center and Department of Medicine, Yale University School of Medicine, New Haven, Connecticut (Dr D. Lee); and the Department of Veterans Affairs Medical Center and Department of Medicine, University of California, Irvine, College of Medicine (Dr Onishi).

Dr D. Lee is now with the Department of Medicine, University of Rochester School of Medicine, Rochester, New York.

This study was supported by the Department of Veterans Affairs Cooperative Studies Program of the Veterans Health Services and Research Administration.

Reprint requests to Maxine A. Papadakis, MD, VA Medical Center 111A1, 4150 Clement St, San Francisco, CA 94121.

ABBREVIATIONS USED IN TEXT

APACHE II = Acute Physiology and Chronic Health Evaluation II
CI = confidence interval
CPR = cardiopulmonary resuscitation
FiO_2 = fractional inspired oxygen
ICU = intensive care unit
PCO_2 = partial pressure of carbon dioxide (tension)
VA = Department of Veterans Affairs

medical schools. All medical patients who received mechanical ventilation during a one- or two-year period (January 1, 1986, to December 31, 1987) were included. Patients were identified from the ICU logs. We excluded patients who were recovering from surgical procedures; those who had been admitted to the ICU primarily for the treatment of a cardiac disorder, such as myocardial infarction or congestive heart failure; or those who had a diagnosis of acquired immunodeficiency syndrome. We also excluded 13 patients who were on long-term ventilatory support at the time of admission to the ICU. For patients with many admissions to the hospital during the study period that required mechanical ventilation, one admission was randomly chosen for inclusion in the study. (In all, 22 patients had two such hospital admissions, and 2 patients had a collective total of nine such admissions). Medical records were available for 88% of eligible patients. These 612 patients constitute the sample for this study.

Data Collection Procedures

Patients were identified at each site from ICU and respiratory care logs. Medical records from the sites were sent to the study coordinating center at the San Francisco, California, VA Medical Center for data abstraction. Chart data were supplemented from on-site computers and laboratory records.

Measurements

Predictor variables. We hypothesized that the following variables would be associated with mortality: advanced age, the use of cigarettes, the use of alcohol, low serum albumin levels, low total lymphocyte counts at the initiation of mechanical ventilation, the initiation of mechanical ventilation after cardiopulmonary resuscitation (CPR), abnormal arterial blood gas values after 24 hours of ventilation, and prolonged duration of mechanical ventilation, ICU, and total hospital stay. Serum albumin levels within a day of the initiation of mechanical ventilation were recorded. (One medical center's routine serum chemistry panel did not include serum albumin levels.) Diagnoses were taken from the discharge summary, patient progress notes, or autopsy report, if available. Repeated episodes of mechanical ventilation during one hospital stay were counted as one unit of observation, and the total days of ventilation were summed. Cardiopulmonary arrest was defined as the cessation of both cardiac and respiratory function.

The APACHE II scoring system, a severity of illness measurement with higher scores associated with higher mortality, was used to compute the predicted death rate for the group.[2] Data for APACHE II were collected for the first 24 hours of an ICU admission. We also calculated a modified APACHE II score that excluded age.

Outcome variable. Determinations of vital status at hospital discharge and at one year were made from the medical records, coroner's report, or the National Death Index.

Analysis

Continuous data were compared by Student's *t* test. Categorical data, including binary data, were tested by the χ^2 statistic. Comparisons with a *P* value of less than 5% (2-tailed) were designated as statistically significant. Logistic regression analyses were used, and the dependent variable was whether the patient was discharged from the hospital (alive). Independent variables include age, serum albumin levels, and APACHE II score. Not every patient had the serum albumin level recorded; those analyses involving serum albumin were done with a reduced data set. Proportional hazards models were used to determine the predictors of one-year mortality.

Results

Most patients were older men (Table 1); 23% were older than 70 years. Smoking and excessive alcohol use were common. Primary diagnoses for admission to an ICU are shown in Table 2. The most common were infection and chronic obstructive pulmonary disease.

In all, 64% of the patients died during the hospital stay (95% confidence interval [CI], 60% to 68%). Within the next year, an additional 84 patients had died (38% of hospital survivors), for a total one-year mortality of 77% (95% CI, 73% to 80%). Mortality rates by diagnoses are

TABLE 1.—*Characteristics of 612 Mechanically Ventilated Medical Patients**

Characteristic	*No. of Patients or Results*	*%*
Male sex	595	97
Age, years	63.3 ± 10.8	--
APACHE II score	26.6 ± 9.2	--
Days in hospital	28.4 ± 38.6	--
Days in ICU	10.8 ± 33.7	--
Days ventilated	7.5 ± 15.1	--
Mean serum albumin level, grams/liter	30.0 ± 7.5	--
Cigarette use		
Ever	503	94
Pack-years	68.7 ± 57.4	--
Current	248	48
Packs/day	1.5 ± 1.4	--
Unknown	75	12
Excessive alcohol use		
Ever	382	78
Current	168	31
Drinks/day	9.7 ± 7.3	--
Unknown		20

ICU = intensive care unit

*Plus-minus values are means ± standard deviation.

TABLE 2.—*Primary Reason for Admission to a Medical Intensive Care Unit*

Diagnosis	Patients, No. (%)	Mortality, No. (%) Hospital	Mortality, No. (%) 1-Year
Sepsis	90 (15)	67 (74)	77 (86)
Infection	89 (14)	48 (54)	62 (70)
Chronic obstructive pulmonary disease	85 (14)	30 (35)	51 (60)
Postcardiac arrest	47 (8)	42 (89)	44 (94)
Gastrointestinal bleeding	45 (7)	39 (87)	42 (93)
Postrespiratory arrest	42 (7)	22 (52)	28 (67)
Aspiration	39 (6)	28 (72)	34 (87)
Neoplasm	29 (5)	23 (79)	26 (90)
Gastrointestinal organ system	24 (4)	19 (79)	20 (83)
Neurologic organ system	22 (4)	18 (82)	19 (86)
Seizure disorder	17 (3)	11 (65)	14 (82)
Respiratory organ disease or other	20 (3)	10 (50)	14 (70)
Intracranial hemorrhage	15 (2)	13 (87)	14 (93)
Drug overdose	14 (2)	0 (0)	2 (14)
Metabolic or renal organ disease	13 (2)	9 (69)	11 (85)
Hemorrhagic shock or hypovolemia	10 (2)	6 (60)	9 (90)
Pulmonary embolus	7 (1)	5 (71)	6 (86)
Asthma	3 (1)	0 (0)	0 (0)
Missing information	1 (0)	1 (100)	1 (100)
Total	612 (100)	391	474

listed in Table 2. There were too few patients with any single diagnosis to determine whether the diagnosis was an independent predictor of outcome; patients with drug overdose, however, had substantially better survival.

Variables Associated With In-hospital Mortality

All variables associated with mortality in univariate analyses (at $P < .05$) are shown in Table 3. Patients who died during the hospital admission had shorter hospital stays (25.5 ± 32.5 days [SD] compared with 33.6 ± 47.2 days, $P = .01$) but a longer duration of mechanical ventilation (8.6 ± 17.1 days compared with 5.6 ± 10.5 days, $P = .004$). Nearly two fifths of nonsurvivors (38%) and 25% of survivors received mechanical ventilation for more than five days ($P < .01$). Arterial blood gas values 20 to 24 hours after mechanical ventilation was initiated in survivors and nonsurvivors still on respirators were similar except for the arterial carbon dioxide pressure (Pco_2), which was significantly higher in survivors (38.8 ± 9.4 mm of mercury compared with 35.3 ± 11.2 mm of mercury, $P < .01$). The Pco_2 was not a good predictor of mortality, however. A third of patients (n = 28) who were receiving an Fio_2 concentration of greater than 50% at 24 hours survived their hospital stay. Increasing age and APACHE II score, lower serum albumin levels, and mechanical ventilation being initiated after CPR were all associated with increased in-hospital mortality (Tables 3 and 4).

Age. Survivors tended to be younger. Hospital mortality among the elderly (>70 years old) was 75% compared with 60% in those younger than 70 years (Tables 3 and 4).

Serum albumin. The serum albumin level had a strong association with hospital mortality (Tables 3 and 4). The hospital mortality for patients with serum albumin levels of less than 25 grams per liter was 82%. Of the two patients with serum albumin levels of less than 20 grams per liter who survived the period in the hospital, one died six weeks after hospital discharge. Of patients with serum albumin levels below 25 grams per liter who died in the hospital, 44% did so within five days of the initiation of mechanical ventilation.

To determine whether serum albumin levels obtained after the initiation of mechanical ventilation were useful in predicting outcome, we examined the variation in serum albumin levels over three consecutive days and found that it was large. In 39 patients in whom serum albumin levels were available on the day preceding, the day of, and the day following the initiation of mechanical ventilation, the mean serum albumin levels fell from 31 to 26 grams per liter. A total of 255 patients had a serum albumin level measured 24 hours after mechanical ventilation was initiated. Of these patients, 60 had serum albumin values below 25 grams per liter, with a hospital and one-year mortality of 75% and 83%, respectively. Patients with serum albumin levels above 25 grams per liter had a hospital and one-year mortality of 57% and 74%, respectively.

To determine whether the serum lymphocyte count could be used as a predictor of outcome for patients in whom serum albumin levels are unavailable, we examined the correlation between the serum albumin level and the absolute lymphocyte count in the three days surrounding mechanical ventilation and found none (correlation coefficient, −.12, −.12, and +.13, respectively).

We determined how many patients with serum albumin levels below 25 grams per liter would meet previously published criteria for a lack of benefit from total parenteral nutrition.[6] We found that 57% of these patients had an APACHE II predicted mortality of greater than 60%, with an actual mortality of 88%. The hospital mortality rate in the remaining patients with serum albumin levels below 25 grams per liter was 71%.

APACHE II score. Higher APACHE II scores were associated with increased hospital mortality (Tables 3 and 4 and Figure 1); 90% of patients with APACHE II scores greater than 35 died in the hospital. Because age is a component of the APACHE II score,[2] we examined age and APACHE II score without age (modified APACHE II) in multivariate models. Each was an independent predictor of outcome.

Cardiopulmonary resuscitation. Patients who were placed on mechanical ventilation after receiving CPR had a hospital mortality of 86% (Tables 3 and 4). None of the 13 patients aged 70 years or older survived the period in hospital when placed on mechanical ventilation after CPR (95% CI, 0% to 28%).

Variables Predictive of One-Year Mortality in Hospital Survivors

Age, APACHE II score, and modified APACHE II score were independent predictors of mortality in the year

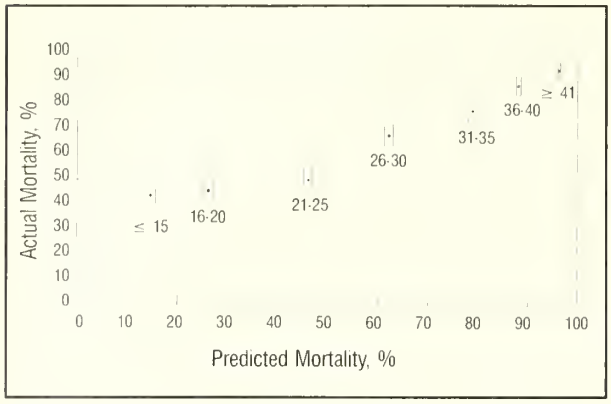

Figure 1.—A calibration chart shows mortality ratios by Acute Physiology and Chronic Health Evaluation II scores. The box around each point indicates standard deviations in both dimensions.

after hospital discharge (Tables 3 and 4). Among those patients who survived their hospital stay, 38% younger than 70 years died within the first year after hospital discharge, for a total one-year mortality of 75%. Of the survivors older than 70 years, 76% died in the year after hospital discharge, for a total one-year mortality of 94% in the geriatric population (95% CI, 88% to 97%). The total one-year mortality for patients whose APACHE II score was higher than 35 was 97% (95% CI, 91% to 99%).

Performance of the APACHE II System for Predicting In-hospital Mortality

The predicted group mortality based on the APACHE II risk equation was 55%, with a 64% actual mortality, for a mortality ratio (actual/predicted) of 1.15. Individual hospital mortality ratios ranged from 0.9 to 1.4. Mortality ratios were also analyzed based on categories of APACHE II scores (Figure 1). With APACHE II scores greater than 20, mortality ratios approached 1 at all hospitals. With APACHE II scores of less than 20, the mean mortality ratio was 2.0 (range 1.0 to 3.1) and was greater than 1.3 in five of the six hospitals (mean 2.3 in the 5 hospitals).

In 17 patients with APACHE II scores of less than 20 and serum albumin levels of less than 25 grams per liter, the hospital mortality was 76%, higher than would have been predicted based on the APACHE II score alone. We used APACHE II scores and serum albumin values in a logistic regression model to predict mortality. As expected, the mean mortality ratio for APACHE II scores of less than 20 improved to 1.2 and approached 1.0 for APACHE II scores of greater than 20. (The following logistic regression equation was used: $Q = -0.86 - [0.08 \cdot \text{APACHE II score}] + [0.73 \cdot \text{serum albumin level from day preceding or of mechanical ventilation}]$, where Q is the natural logarithmic odds of mortality.)

Discussion

The in-hospital mortality for medical patients who received mechanical ventilation in the six VA medical centers in our study was 64%. Of those who survived the period in the hospital 38% died within the first year, bringing the total one-year mortality to 77%. Mortality was even higher among patients older than 70 years: three in four of these patients died during the initial hospital stay, and the one-year mortality was 94%. Four variables were independently associated with increased in-hospital

TABLE 3.—*Variables Associated With In-hospital Mortality and, for Those Patients Who Survived Hospital Admission, 1-Year Mortality*

	In-hospital Mortality				*1-Year Mortality*			
Variable	*No.*	*Odds Ratio*	*(95% CI)*	*P Value*	*No.*	*Hazard Ratio*	*(95% CI)*	*P Value*
Univariate Model								
Days in hospital/day increase	611	0.99	(0.99-1.00)	.02	220	1.0	(1.0-1.0)	.57
Days ventilated/day increase	607	1.02	(1.00-1.04)	.02	219	1.0	(1.0-1.0)	.59
Age/10-year increase	612	1.3	(1.1-1.6)	<.001	220	1.8	(1.4-2.1)	<.001
Serum albumin level/ 10 grams-per-liter decrease	320	2.3	(1.6-3.2)	<.001	105	1.1	(0.7-1.5)	.79
APACHE II score/10 point increase	571	2.7	(2.1-3.5)	<.001	210	1.8	(1.4-2.4)	<.001
Modified APACHE II score*	571	2.6	(2.1-3.4)	<.001	210	1.7	(1.3-2.2)	<.001
Cardiopulmonary resuscitation	606	3.9	(2.1-7.3)	<.001	219	0.6	(0.2-1.5)	.25
Pco_2/5 mm-of-mercury decrease	309	1.2	(1.1-1.3)	.007	127	1.0	(0.9-1.1)	.66
Multivariate Models								
Model 1								
Serum albumin level/ 10 grams-per-liter decrease	308	2.1	(1.5-3.1)	<.001	101	1.0	(0.7-1.4)	.81
Modified APACHE II score*	308	2.2	(1.5-3.1)	<.001	101	1.2	(0.7-1.9)	.56
Age/10-year increase	308	1.2	(1.0-1.5)	.129	101	1.8	(1.3-2.6)	<.001
Model 2								
Modified APACHE II score*	571	2.6	(2.0-3.3)	<.001	210	1.6	(1.2-2.1)	.001
Age/10-year increase	571	1.3	(1.1-1.6)	.001	210	1.9	(1.5-2.3)	<.001

APACHE II = Acute Physiology and Chronic Health Evaluation II, CI = confidence interval, Pco_2 = partial pressure of carbon dioxide.

*Per 10-point increase.

TABLE 4.—*Variables Associated With In-hospital and 1-Year Mortality*

	In-hospital				1-Year		
Variable	*No.*	*No. Dead*	*(%)*	*(95% CI)*	*No. Dead*	*(%)*	*(95% CI)*
Age, years							
<60	180	108	(60)	53-67	127	(71)	64-77
60-69	294	178	(61)	55-67	230	(78)	73-82
70-79	113	86	(76)	67-83	106	(94)	87-97
80-89	21	16	(76)	52-91	20	(95)	74-100
>89	4	3	(75)	22-99	4	(100)	40-98
Serum albumin level, grams/liter							
<20	24	22	(92)	72-99	23	(96)	77-100
20-25	48	37	(77)	62-87	41	(85)	71-93
26-30	81	59	(73)	62-82	67	(83)	73-90
>30	167	97	(58)	50-66	126	(75)	68-81
APACHE II score							
≤15	50	22	(44)	29-59	28	(56)	41-71
16-20	104	48	(46)	36-56	63	(61)	51-71
21-25	129	64	(50)	41-59	98	(76)	67-83
26-30	110	75	(68)	59-77	97	(88)	80-93
31-35	73	57	(78)	66-86	66	(90)	80-95
36-40	57	50	(88)	76-95	54	(95)	85-99
>40	48	45	(94)	82-98	48	(100)	91-100
Cardiopulmonary resuscitation							
Yes	83	71	(86)	76-92	75	(90)	81-95
No	523	316	(60)	56-64	406	(78)	74-81

APACHE II = Acute Physiology and Chronic Health Evaluation II, CI = confidence interval

mortality: age, serum albumin levels, APACHE II scores, and the initiation of mechanical ventilation after CPR.

Many older veterans received mechanical ventilation; nearly a quarter of our patients were older than 70. Several studies have shown that age is a predictor of disability or death from mechanical ventilation.[7,8] We also found that advancing age increased the risk of dying in hospital and the one-year mortality.

Our findings confirm previous ICU studies showing that the serum albumin level is an important prognostic variable.[5,9-12] Hospital mortality for patients with serum albumin levels of less than 25 grams per liter was more than 80%, with a one-year mortality approaching 90%. The one-year mortality rose to 96% if the serum albumin level was below 20 grams per liter.

One can argue that a low serum albumin level should be used as a predictor of a poor prognosis only if an improvement in nutrition does not improve the patient's condition, yet the benefit of parenteral nutrition remains controversial.[13] It would be problematic to extrapolate results from the recent VA cooperative study on the role of total parenteral nutrition in surgical patients to our medical patients.[13,14] Also, nearly half of our patients with hypoalbuminemia who died did so within five days of the initiation of mechanical ventilation, making it unlikely that aggressive alimentation would have affected the outcome. Other investigators have used APACHE II scores to differentiate ICU patients who would not benefit from total parenteral nutrition.[6] These include patients with at least a 60% risk of death after ICU admission. In all, 57% of our patients with a serum albumin level of less than 25 grams per liter met this criterion. Further studies on the role of nutritional intervention would be useful.

Several nutritional studies have shown a correlation between serum lymphocyte counts and serum albumin levels.[15] We looked at whether the absolute lymphocyte count could be used as a prognostic variable if serum albumin levels were unavailable, but could show no correlation of serum lymphocyte counts to serum albumin levels or to mortality rate.

In our study, veterans who were placed on mechanical ventilation after CPR had the same 14% survival rate as was seen among patients who received CPR in a university hospital.[16] Elderly patients are least likely to benefit from CPR.[17] As in a study from the Houston VA Medical Center, none of our hospital survivors were older than 70 years.[18]

Our study confirms that the APACHE II scoring system performs well in predicting outcome for individual hospitals and the group as a whole among veterans receiving intensive care who are mechanically ventilated. Mortality ratios (actual to predicted mortality) based on APACHE II scores have been used to evaluate results in ICUs.[19] Among our sickest patients (APACHE II scores greater than 20), the observed hospital death rates were consistent with those predicted from APACHE II, suggesting that the quality of care was acceptable in VA medical centers. At APACHE II scores of below 20, however, actual mortality exceeded predicted mortality in five of six hospitals. There are at least two explanations for this

calibration discrepancy. The first is that the discrepancy is due to a poor quality of care. The increased mortality ratios were seen in five of the six hospitals for the low scores, but in none of the six for higher APACHE II scores. The second explanation for the calibration discrepancy is selection bias. Our study protocol focused only on the "sickest" patients, whereas the APACHE system is based on all ICU patients. This differential selection may explain the higher hospital mortality ratios in our mechanically ventilated patients with low APACHE II scores. Knaus and co-workers showed a similar rise in predicted death rates when focusing on a special group that differs in case selection from the original APACHE II method.[1] Others have found increased mortality ratios in patients with complications (unintended, harmful occurrence resulting from a therapeutic intervention) and those not admitted to an ICU directly from an emergency department.[20,21] This study has identified an additional category of discrepant mortality ratios, that being ventilated medical patients with APACHE II scores of less than 20. Nonetheless, these discrepancies do not reduce the usefulness of the APACHE II scoring system, as it discriminates well, especially at the higher ranges where most of these mechanically ventilated patients scored.

We could not validate the clinical usefulness of arterial blood gas values after the initiation of mechanical ventilation for predicting outcome.[5] Hypocarbia or an Fio_2 of greater than 50% after 24 hours has previously been associated with a poor prognosis.[5,22] Although these variables were found statistically more frequently in our nonsurvivors, as many as a third of patients with these values survived the period in the hospital.

This study has several limitations. Data were obtained from chart review. Postoperative patients or those admitted to the ICU primarily for the treatment of a cardiac disorder were excluded from the study. We may have underestimated the frequency of current alcohol abuse or cigarette use. Serum albumin levels were missing in half the patients. Data on the primary diagnosis were missing in a few patients for whom only parts of the medical record were available. Vital status at hospital discharge and after one year were available in all patients, however. Last, this study in veterans may not be generalizable to patients in other settings.

This study does not answer the question of who will and who will not benefit from mechanical ventilation, but it does identify a subset of this relatively homogeneous population in whom mechanical intervention has a poor outcome and is possibly futile. Although there is no agreement on what constitutes futility or a level of prognosis poor enough to urge withholding intervention,[23-27] a one-in-ten chance of survival may be adequate justification for the continued use of ICU resources, but may be unacceptable if resources become scarcer. We hope these findings aid clinicians, patients, and families in making decisions about this life-sustaining therapy.

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Articles

Is Being a Doctor Still Fun?

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Over the past two decades, a decline in physician job and career satisfaction has been reported. This study was developed to determine the current state of physician satisfaction and to define factors correlated with overall satisfaction. We mailed a survey to 406 physicians in Solano County, California. Responses were anonymous, and data were analyzed by several methods. Of the 406 physicians, 251 (62%) responded. Most respondents were satisfied with their jobs (80%). The vast majority felt good about their ability to help their patients (92%), enjoyed the relationships they had with patients (93%) and colleagues (86%), and found their work intellectually satisfying (89%). Nearly two thirds (63%) of respondents thought their job was "fun." This ability to derive great pleasure from work showed the strongest correlation with overall satisfaction. Overall satisfaction did not differ between primary care and non-primary care physicians or between physicians in a large health maintenance organization and those in mostly solo and small-group fee-for-service practices. Despite substantial challenges to physician morale and autonomy, most responding physicians in our study continued to enjoy overall job satisfaction, and a solid majority thought that their work was fun.

(Chuck JM, Nesbitt TS, Kwan J, Kam SM: Is being a doctor still fun? West J Med 1993; 159:665-669)

The decade of the 1970s is frequently cited as a period of high job and career satisfaction for physicians. In a 1973 survey of 2,700 physicians, 85.6% had "no doubt at all" about their career choice.[1] During this time, a popular television series, "Marcus Welby, MD," enhanced the public image of physicians by portraying a caring family doctor who enjoyed the respect of his colleagues and the adoration of his community.

In the past two decades this level of physician satisfaction has reportedly declined, most notably among established primary care providers.[2] Gallup polls conducted for the American Medical Association in 1989 and 1990 showed that only 60% of physicians interviewed would definitely or probably enter medical school again.[3] Major factors identified by disgruntled physicians in these and other surveys include the following: changes in methods of reimbursement leading to increased paperwork and decreased income; government and insurance company regulations interfering with physician autonomy in decision making; and a deterioration of the physician-patient relationship, marked by a decrease in patient respect for physicians and an increase in the number of malpractice lawsuits.[1-5]

What is the current status of physician job and career satisfaction? Is it true, as Lacsamana has suggested, that for many physicians, practicing medicine is no longer fun?[6] Also, in our climate of reimbursement hassles, lawsuits, and decreased patient trust, which factors are most closely associated with overall job satisfaction? To help answer these questions, we present the results of a physician survey conducted in the spring of 1992.

Methods and Study Group

Our study group included physicians from Solano County, which is located in northern California between Sacramento and San Francisco. This county's ethnically diverse population of 340,421 and balance between rural farmlands and more urbanized settings make it representative of many American communities. We sent 406 physicians a questionnaire designed to assess satisfaction with various aspects of their work. Names and addresses were obtained from the membership roster of the Solano County Medical Society (SCMS physicians, n = 152) and the staff roster of the Kaiser Permanente Hospital in Vallejo, California (Permanente Medical Group [PMG] physicians, n = 254). The many PMG physicians who were members of the medical society were counted as PMG physicians. All responses were anonymous to encourage physician participation and candor of responses. For this reason, information on nonrespondents is not available. The questionnaire used a 7-point scale ranging from 1 (disagree strongly) to 7 (agree strongly), with 4 representing neutral, to indicate how much the respondents agreed with each item.

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ABBREVIATIONS USED IN TEXT

PMG = Permanente Medical Group
SCMS = Solano County [California] Medical Society

Correlational analyses were done to determine whether a statistically significant relationship existed at $P < .01$ between overall job satisfaction and ratings on various aspects of a physician's job and career. Data were also evaluated with a principal components factor analysis with Varimax rotation to determine the facets of satisfaction as represented by the items in our survey. In addition, *t* tests were conducted to determine whether there were statistically significant differences at $P < .01$ in ratings given by primary care versus non-primary care physicians and PMG versus SCMS physicians.

Results

A total of 251 physicians returned completed questionnaires, for an overall response rate of 62%. Primary care physicians (family practice, general practice, internal medicine, and pediatrics) comprised 42% of our respondent group and responded at a higher rate than non-primary care physicians (74% versus 55%). The Permanente Medical Group physicians comprised 65% of our respondents and responded at a slightly higher rate than their SCMS colleagues (65% versus 57%). On average, respondents were 44 years old and had been in practice for 12 years. The PMG respondents worked in a prepaid group model health maintenance organization. Of the 87 non-PMG respondents, the large majority (70, or 80%) described their practice as predominantly fee for service, preferred provider organization, individual practice association, and the like. Of these 87 respondents, a third were in solo practice, slightly less than a third in five-plus-person multispecialty groups, and a quarter in two- to four-person single-specialty groups.

Most of the respondents felt that overall they were sat-

TABLE 1.—*Respondents Who Agreed With the Following Statements Related to Physician Job and Career Satisfaction**

Questionnaire Item	*Respondents, %*
Satisfaction and 'Value' of Being a Physician	
Overall, I am satisfied with my job	80
I feel good about my ability to cure, heal, and help my patients	92
My work is intellectually satisfying	89
I have sufficient opportunities for professional growth	57
My job is "fun"	63
My job is prestigious	63
In retrospect, the personal sacrifices I made during medical training were worthwhile	65
In retrospect, the financial debts I accumulated during medical training were worthwhile	61
Knowing what I know now, I would choose to be a physician again	67
Knowing what I know now, I would choose my specialty again	70
I would encourage my child to pursue a career in medicine	44
Relationships	
I enjoy the relationships I have with my patients	93
I enjoy the relationships I have with my colleagues and consultants	86
I enjoy the relationships I have with my support staff	90
I enjoy a meaningful personal and family life	83
Working Conditions	
I am satisfied with my amount of weekend and night duty	60
I have control over my work environment	45
I have control over the number of hours I work	47
I worry about contracting a serious infectious disease, eg, AIDS [acquired immunodeficiency syndrome], in the course of my work	45
Business and Administrative Issues	
The future of my job is secure and predictable	65
Physician malpractice premiums are too high	67
My fear of being sued adversely alters the way I practice medicine	58
I have lost a significant amount of control over patient care due to regulatory agencies	52
I have too many administrative duties	34
I have too many business worries	28
Compensation and Benefits	
I am satisfied with my financial compensation	72
I am satisfied with my benefits	82
I am satisfied with my retirement plan	75

*Results reflect the percentage of respondents who rated the statement a 5, 6, or 7 on the 1 to 7 scale. All items were answered by at least 80% of respondents.

TABLE 2.—*Correlations of Various Questionnaire Items With Overall Job Satisfaction*

Questionnaire Item	*Correlation Coefficient**
My job is "fun"	.67
Knowing what I know now, I would choose to be a physician again	.51
My work is intellectually satisfying	.48
I have control over my work environment	.48
I enjoy the relationships I have with my colleagues and consultants	.47
I would encourage my child to pursue a career in medicine	.46
In retrospect, the financial debts I accumulated during medical training were worthwhile	.45
I have control over the number of hours I work	.44
My job is prestigious	.43
In retrospect, the personal sacrifices I made during medical training were worthwhile	.42
I feel good about my ability to cure, heal, and help my patients	.41
I am satisfied with my financial compensation	.39
I enjoy the relationships I have with my support staff	.36
Knowing what I know now, I would choose my specialty again	.35
I have sufficient opportunities for professional growth, eg, teaching, research, continuing medical education	.34
I enjoy the relationships I have with my patients	.31
The future of my job is secure and predictable	.30
I am satisfied with my benefits	.29
I enjoy a meaningful personal and family life	.27
I am satisfied with my amount of weekend and night duty	.27
I am satisfied with my retirement plan	.23
My fear of being sued adversely alters the way I practice medicine	−.22

*All correlations are significant at the $P < .01$ level or less. A correlation is a statistic that ranges in absolute value from 0 to 1. It describes the strength of the relationship between 2 continuous variables, with a correlation of 1 being a "perfect" relationship.

isfied with their jobs (Table 1). A large majority felt good about their ability to help their patients and that their work was intellectually satisfying. A solid majority thought that their job was fun, and an equal proportion felt their job was prestigious. Two thirds of respondents indicated that they would choose to be a physician again and more than two thirds that they would choose their specialty again. A large majority of respondents enjoyed good relationships with their patients, their colleagues and consultants, and their support staff. In addition, most felt that they had a meaningful personal and family life.

The three items on the questionnaire that demonstrated the strongest relationship with overall job satisfaction were related to the satisfaction and "value" of being a physician (Table 2). Physicians who felt that their work was fun, would choose to be a physician again, and found their work to be intellectually satisfying were much more likely to report overall job satisfaction. Fear of being sued that led physicians to adversely alter their style of practice was correlated with lower job satisfaction, but the correlation coefficient was small. Further evaluation of our data with a principal components factor analysis supported the finding that survey items related to the intrinsic satisfaction of being a physician (satisfaction with the work itself) were more strongly related to overall job satisfaction than were extrinsic factors (such as satisfaction with pay and benefits) ($r = .66$ and .30, respectively, $P < .05$). Finally, multiple regression analysis showed that the facets of job satisfaction represented in the survey accounted for a large amount (51%) of the observed variance in overall job satisfaction.

Comparison of Primary Care and Non-Primary Care Physicians

Overall, there were few differences in the average responses between primary care and non-primary care physicians (Table 3). Non-primary care physicians tended to agree more strongly that they worry about contracting a serious infectious disease at work; that they would choose their specialty again; and that they feel good about their ability to cure, heal, and help their patients. These differences, although statistically significant, were relatively small.

Comparison of Solano County Medical Society and Permanente Medical Group Physicians

The largest difference noted between the SCMS and the PMG physicians was that, on the average, the SCMS physicians agreed and PMG physicians disagreed that physicians had too many business worries, had lost a substantial amount of control over patient care because of regulatory agencies, and had too many administrative duties (Table 3). The SCMS physicians tended to concur more strongly that they had control over their work environment and the number of hours they worked. The PMG physicians felt more strongly that the future of their jobs was secure and predictable and that they were more satisfied with issues related to compensation and benefits.

Summary and Discussion

Despite recent negative publicity about medical careers, most physicians in our respondent group were satisfied with their jobs. This global satisfaction is important

TABLE 3.—*Mean Ratings for Primary Care Versus Non-Primary Care Physicians and Permanente Medical Group (PMG) Versus Solano County Medical Society (SCMS) Physicians on Statements Related to Career Satisfaction**

Questiannaire Item	*Average Total Sample Rating*	*Average Primary Care Rating*	*Average Non-Primary Care Rating*	*Average PMG Rating*	*Average SCMS Rating*
Satisfaction and 'Value' of Being a Physician					
Overall, I am satisfied with my job	5.34	5.21	5.45	5.36	5.31
I feel good about my ability to cure, heal, and help my patients	5.92	(5.70)	(6.10)	5.89	5.97
My work is intellectually satisfying	5.66	5.58	5.73	5.59	5.80
I have sufficient opportunities for professional growth, eg, teaching, research, continuing medical education	4.46	4.39	4.52	4.27	4.80
My job is "fun"	4.60	4.42	4.74	4.65	4.49
My job is prestigious	4.80	4.73	4.85	4.80	4.80
In retrospect, the personal sacrifices I made during medical training were worthwhile	4.85	4.81	4.88	4.94	4.67
In retrospect, the financial debts I accumulated during medical training were worthwhile	4.90	4.78	5.00	5.01	4.69
Knowing what I know now, I would choose to be a physician again	4.94	5.03	4.87	5.15	4.55
Knowing what I know now, I would choose my specialty again	5.15	(4.79)	(5.44)	5.30	4.85
Relationships					
I enjoy the relationships I have with my patients	5.94	5.94	5.94	5.92	5.98
I enjoy the relationships I have with my colleagues and consultants	5.64	5.51	5.75	5.73	5.47
I enjoy the relationships I have with my support staff	5.69	5.68	5.70	5.59	5.88
I enjoy a meaningful personal and family life	5.70	5.73	5.68	(6.00)	(5.13)
Working Conditions					
I am satisfied with my amount of weekend and night duty	4.71	4.67	4.74	(4.98)	(4.20)
I have control over my work environment	3.85	3.61	4.05	(3.49)	(4.54)
I have control over the number of hours I work	4.02	3.95	4.08	(3.74)	(4.56)
I worry about contracting a serious infectious disease, eg, AIDS [acquired immunodeficiency syndrome], in the course of my work	3.96	(3.53)	(4.31)	3.96	3.97
Business and Administrative Issues					
The future of my job is secure and predictable	4.74	4.83	4.66	(5.31)	(3.65)
Physician malpractice premiums are too high	5.23	5.29	5.18	5.17	5.33
My fear of being sued adversely alters the way I practice medicine	4.50	4.54	4.46	4.39	4.71
I have lost a significant amount of control over patient care due to regulatory agencies, eg, CMRI [California Medical Review, Inc] (Medicare), Medi-Cal, and the like	4.40	4.44	4.36	(3.50)	(5.98)
I have too many administrative duties	3.81	3.75	3.85	(3.14)	(5.05)
I have too many business worries	3.27	3.28	3.27	(2.25)	(5.17)
Compensation and Benefits					
I am satisfied with my financial compensation	5.13	5.13	5.12	(5.49)	(4.45)
I am satisfied with my benefits	5.58	5.72	5.47	(6.08)	(4.64)
I am satisfied with my retirement plan	5.32	5.39	5.27	(5.94)	(4.07)

*Respondents used a 7-point scale ranging from 1 (disagree strongly) to 7 (agree strongly), with 4 representing neutral to indicate how much they agreed with each item. Significant differences between average ratings by primary care and non-primary care physicians and PMG and SCMS physicians ($P < .01$) are shown in parentheses.

as it has been associated with increased physician retention and could arguably lead to higher morale, enhanced productivity, and improved quality of care.[7] It is encouraging that most respondents also felt that their job was fun. This suggests that whereas the recent demoralization of the medical profession is definitely real, perhaps its severity and effect on individual physicians have been overstated. The finding that having fun at work demonstrated the strongest correlation with overall job satisfaction suggests that efforts directed at helping physicians to derive enjoyment from their work may be of paramount importance if the goal is to improve overall job satisfaction.

Our comparison of primary care and non-primary care physicians refutes the statement that most primary care physicians perceive themselves to be, and are, overworked, underpaid, and underrecognized for their efforts. Our primary care respondents showed comparable overall satisfaction, intellectual satisfaction, and prestige with their subspecialty colleagues. This is an important finding for those groups interested in increasing the number of generalists in this country. Current efforts to achieve this goal emphasize altering medical student selection and training and improving practice conditions and economic rewards for generalists.[8] The long-term success of these efforts is equally dependent on students choosing careers in primary care because they are convinced by practicing physicians, such as those in our study, that this type of career will be rewarding and satisfying.

The overall job satisfaction enjoyed equally by our SCMS and PMG respondents contrasts with earlier studies from the 1970s that suggested a higher level of satisfaction among physicians in solo and small-group fee

for-service practices.[9] We think that the main reason for this change is that physicians in smaller groups are facing an increasing burden of business and administrative problems; meanwhile, their colleagues in larger prepaid groups remain relatively insulated from these problems by their economy of scale, centralization of support services, and methods of reimbursement.

Finally, the finding that 67% of respondents would choose to be physicians again is encouraging. This percentage compares favorably with a random sample of 685 employed adults in which only 44% of respondents said they would have chosen their same line of work (Gallup Poll, May 1988, for Accountants on Call). In Wolfgang's study, physicians (77%) were more likely than nurses (64%) and pharmacists (55%) to choose their professions again.[10] We conclude that despite considerable challenges to physician morale and autonomy, medicine continues to be a relatively satisfying and desirable career choice for most physicians in our respondent group. A larger national study of physician satisfaction that includes a more representative sample of practice settings would be helpful in determining whether our findings accurately reflect the attitudes of physicians in other parts of the country.

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Conferences and Reviews

Novel Antithrombotic Therapy

Discussant
GEORGE M. RODGERS, MD, PhD

This discussion was selected from Medical Grand Rounds in the Department of Medicine, University of Utah School of Medicine, Salt Lake City, on January 6, 1993. Taken from a transcription, it has been edited by William D. Odell, MD, PhD, Professor and Chair, Department of Medicine.

WILLIAM ODELL, MD: *Internal medicine is a fast-moving specialty. If the word "hirudin" and the words "low-molecular-weight heparin" mean nothing to you, you are already outdated. We have asked George Rodgers, MD, to update us on novel antithrombotic therapy.*

GEORGE M. RODGERS, MD*: I will discuss the relevance of ticks, leeches, snakes, and vampire bats in the medical therapy for thrombotic disease. The salivary gland secretions of ticks, leeches, and vampire bats and the venom gland secretions of certain pit vipers contain chemical compounds that maintain blood fluidity while these creatures suck blood from their host or, in the case of snake venom, inhibit blood coagulation to permit the entry of toxins into the bloodstream of the prey. The isolation of certain hemostatically active components from these secretions has led to clinical trials with promising results, indicating that many of these agents may substantially enhance the current therapy for venous and arterial thrombosis.

I provide a brief overview of the currently available antithrombotic agents—heparin, warfarin, aspirin, and ticlopidine—and recommendations for their use and an introduction and clinical status report of the new antithrombotic agents, some of which will soon be available.†

Available Antithrombotic Agents

Heparin

Commercial heparin is a heterogeneous mixture of polysaccharides, especially sulfated glucosamine and uronic acid residues. Unfortunately, most of the polysaccharides contained in commercial heparin preparations are not active in inhibiting coagulation. Heparin requires the plasma protein cofactor antithrombin III to express anticoagulant activity; this occurs by heparin binding both antithrombin III and activated coagulation proteases, such as thrombin, to catalyze the protease inhibition by antithrombin III. Heparin is currently used for the prophylaxis and treatment of venous thromboembolism, unstable angina, acute myocardial infarction, and chronic disseminated intravascular coagulation. The standard prophylactic heparin regimen is 5,000 U 2 hours before an operation, then 5,000 U every 8 to 12 hours until the patient is up and walking.[1] The therapeutic use of heparin requires the drug to be given in sufficient dosage to prolong a clotting test, usually the activated partial thromboplastin time (aPTT), between 1½ and 2½ times the mean laboratory control value. Laboratories should calibrate their aPTT assay so that the therapeutic range is equivalent to heparin concentrations of 0.2 to 0.4 U per ml. Therapeutic heparin administration usually involves an intravenous bolus dose (5,000 to 10,000 U) to achieve instantaneous anticoagulation, followed by a continuous infusion rate of 32,000 U per 24 hours; subsequent infusion rates are adjusted by measuring the aPTT values at six-hour intervals until a therapeutic aPTT value is achieved.[2]

A nomogram approach to achieve rapid anticoagulation has recently been proposed.[3] The importance of attaining rapid heparin anticoagulation has been emphasized in studies noting an increased risk of recurrent thromboembolism in patients not rapidly anticoagulated.[4] Other studies suggest that routine proximal venous thrombosis can be adequately treated with heparin for five days.[5] Extensive deep venous thrombosis or pulmonary embolism probably requires seven to ten days of heparin therapy.

Warfarin Sodium

Warfarin sodium is the primary oral anticoagulant used in the United States. Warfarin induces vitamin K deficiency by inhibiting the hepatic vitamin K cycle, resulting in deficient synthesis of prothrombin and factors VII, IX, and X. Because the anticoagulant effect of warfarin requires four to five days before levels of the vitamin K-dependent coagulation proteins are optimally reduced, patients need at least five days of heparin overlap therapy with warfarin.[6] Starting warfarin therapy on day 1 of heparin therapy may decrease the incidence of heparin-associated thrombocytopenia or thrombosis.[7]

Because the anticoagulant effect of warfarin can be affected by multiple factors, including diet, liver disease,

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†See also the editorial by Z. M. Ruggeri, MD, "Role of Platelet Adhesion and Aggregation in Antithrombotic Therapy" on pages 702-704.

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ABBREVIATIONS USED IN TEXT

aPTT = activated partial thromboplastin time
LMW = low molecular weight
t-PA = tissue-plasminogen activator

and other medications, close laboratory monitoring of warfarin therapy is important. Standardization of the prothrombin time assay is a major issue in correct laboratory monitoring of oral anticoagulant therapy. The realization that most laboratories in the United States use insensitive prothrombin (thromboplastin) reagents and the variability of commercial reagents in detecting vitamin K deficiency led to recommendations to adopt the international normalized ratio to standardize the prothrombin time assay.[8]

Recommendations for the intensity of warfarin therapy have been recently modified (Table 1). These recommendations are based on studies indicating that arterial embolism and prosthetic metal heart valves require a lower intensity of oral anticoagulation than previously thought. The recommended intensity of therapy for venous thromboembolism remains unchanged.[8]

TABLE 1.—*Recommended Therapeutic Range for Warfarin Therapy**

Indication	*International Normalized Ratio (INR)†*
Treatment of venous thrombosis Treatment of pulmonary embolism Prevention of systemic embolism Tissue heart valves Acute myocardial infarction Atrial fibrillation	2.0-3.0
Recurrent embolism Mechanical heart valves	2.5-3.5

*From Hirsh et al.[8]
†Warfarin intensity is given in the INR format. The INR is a standardized method of reporting prothrombin times to ensure that a uniform intensity of oral anticoagulant therapy is used worldwide.

Aspirin

Aspirin inhibits platelet function by irreversibly acetylating platelet cyclooxygenase, resulting in diminished prostaglandin and thromboxane A_2 formation. Aspirin is currently being used to treat stable and unstable angina and for the secondary prevention of acute myocardial infarction, transient ischemic attacks, thrombotic stroke, and peripheral arterial disease. The primary prevention of myocardial infarction is a controversial indication. The recommended dosage of aspirin for these indications is 160 to 325 mg per day; patients with cerebrovascular disease may benefit from a higher dosage.[9]

Ticlopidine Hydrochloride

Ticlopidine hydrochloride inhibits the adenosine diphosphate-induced activation of the platelet fibrinogen receptor and can be used as a substitute for aspirin in patients unable to take aspirin or for whom aspirin therapy has failed, especially those with cerebrovascular disease. The standard dosage of ticlopidine is 250 mg twice a day. The important toxic effect of ticlopidine is neutropenia, which occurs in about 1% of patients taking the drug and may require discontinuing its use.[9,10]

Novel Antithrombotic Agents

A rationale for the development and use of the new antithrombotic agents (Table 2) is that commercial heparin is not an ideal anticoagulant. About 7% of patients treated with heparin for venous thromboembolism will have recurrent thrombosis.[5] Patients receiving heparin for arterial thrombosis (angioplasty, acute myocardial infarction) have an even greater rate of rethrombosis, from 5% to 20%.[11] In addition to this failure rate, heparin use is associated with certain toxic effects (thrombocytopenia, arterial thrombosis, osteoporosis).[2] Consequently, it would be desirable to have available more potent antithrombotics that are associated with fewer adverse effects. Compared with commercial heparin, the novel anticoagulants are more efficient inhibitors of thrombin (or other activated coagulation proteases); the activity of these agents is not dependent on antithrombin III, and these novel anticoagulants can inhibit thrombin bound to the clot. One of the first studies indicating a superior therapeutic effect of the new anticoagulants compared a tripeptide inhibitor of thrombin, D-phenylalanyl-L-prolyl-L-arginyl (Phe-Pro-Arg)-chloromethyl ketone, with heparin in a baboon vascular graft model. This synthetic antithrombin, but not heparin, abolished platelet-dependent arterial thrombosis, suggesting that thrombin was important not only in fibrin clot formation, but also in platelet activation and thrombosis.[12]

Another study demonstrated the advantages of another novel agent, hirugen (an analogue of hirudin, discussed later), in inhibiting clot-bound thrombin activity. Hirugen was able to inhibit thrombin equally well in the fluid and solid phases. Heparin, however, even at a concentration of 4 U per ml (a tenfold greater concentration than that required to treat venous thromboembolism) was unable to completely inhibit clot-bound thrombin.[13] Thus, these studies provided a basis for explaining why these agents show superior antithrombotic efficacy.

TABLE 2.—*Novel Antithrombotic Agents*

- Anticoagulants
  - D-Phenylalanyl-L-prolyl-L-arginyl chloromethyl ketone
  - Low-molecular-weight heparin
  - Heparinoids
  - Hirudin
  - Tick anticoagulant peptide
  - Antistasin
- Antiplatelet agents
  - Glycoprotein IIb-IIIa peptides (disintegrins)
  - Monoclonal antibody to glycoprotein IIb-IIIa
  - Glycoprotein Ib peptides
  - Ridogrel
- Fibrinolytic agents
  - Tissue-plasminogen activator mutants
  - Vampire bat-plasminogen activator

TABLE 3.—*Treatment Regimens With Enoxaparin**

Patient Use	*Subcutaneous Dosage†*
Prophylaxis	
Medical patients	60 mg (4,800 U) daily
General surgery	20 mg (1,600 U) daily
Hip surgery	30 mg (2,400 U) twice a day or 40 mg (3,200 U) daily
Therapy	70 mg (5,600 U) twice a day‡

*From Hirsh and Levine.[14]
†Dosages for this low-molecular-weight heparin that is given subcutaneously are listed both on a weight basis and in terms of anti-factor Xa units.
‡Based on 2 mg/kg a day in divided doses.

Novel Anticoagulants

New antithrombotic agents related to heparin include low-molecular-weight (LMW) heparin and heparinoids.[14] Low-molecular-weight heparins are isolated from commercial heparin preparations by chemical or enzymatic methods; these drugs are more homogeneous than commercial heparin and possess higher specific activity. Heparinoids are LMW glycosaminoglycans related to, but distinct from, heparin (dermatan sulfate, chondroitin sulfate). It is thought that LMW heparins inhibit thrombosis by primarily inhibiting factor Xa, not thrombin. Low-molecular-weight heparins possess a half-life twice that of commercial heparin and a threefold greater bioavailability after a subcutaneous injection. These favorable pharmacokinetic properties mean that the agents can be given at a fixed daily dosage, on a body weight basis, subcutaneously, and without the need for laboratory monitoring. A disadvantage of their use is that they are not therapeutically equivalent; optimal dosages and treatment intervals will differ with each preparation.[14]

Clinical studies with LMW heparins indicate superiority over commercial heparin in both the prophylactic and therapeutic settings.[14] They were more protective than heparin in preventing venous thromboembolism in orthopedic patients[15] and in medical patients[16]; therapeutically, LMW heparin was superior to standard heparin in preventing the recurrence of venous thrombosis in patients with established disease (3% versus 7%).[17] In addition, it appears that their use is associated with fewer episodes of hemorrhage (0.5% versus 5%).[17]

Three LMW heparins are in clinical trials in the United States. One of these drugs, enoxaparin (Lovenox), has just been released for clinical use, and two others (Fragmin [dalteparin] and Normiflo [Rd heparin]) are in phase III trials. The standard indication for these agents will be for prophylaxis of venous thrombosis in high-risk (orthopedic) patients and for the treatment of established deep venous thrombosis. Table 3 summarizes the likely dosage regimens to be used with enoxaparin.[14]

Two other classes of novel anticoagulants are specific inhibitors to thrombin or factor Xa. In terms of thrombin inhibitors, the most promising agents are hirudin and its analogues. Hirudin is a natural salivary secretion of the European medicinal leech (*Hirudo medicinalis*, Figure 1). The medicinal leech was used centuries ago for bloodletting. The leech has been used recently to reduce venous congestion following certain surgical procedures. Hirudin is a 65-amino acid peptide that binds specifically and irreversibly to thrombin to inactivate the enzyme. It does not require antithrombin III for activity.[18,19] Recombinant hirudin is being studied in clinical trials, as are recombinant hirudin analogues (hirugen, hirulog, Table 4).

Figure 1.—*Hirudo medicinalis,* the medicinal leech, is the source of natural hirudin. This leech grows to an average length of 2.5 to 5 cm (1 to 2 in) and is used currently to restore venous circulation in patients who have had cosmetic and reconstructive surgical procedures. Recombinant analogues of hirudin are available for clinical trials. (This photograph was provided by Marie Bonazinga, Leeches USA, Ltd.)

Investigations of animal models of arterial thrombosis provided strong evidence for the efficacy of hirudin in preventing the recurrence of arterial clots.[20,21] In these models, hirudin was more effective than heparin, aspirin, or other antiplatelet drugs. In terms of clinical trials, hirudin is now in phase III studies to evaluate the treatment of venous thrombosis, arterial thrombosis, hemodialysis, disseminated intravascular coagulation, angioplasty, coronary artery bypass surgery, unstable angina, and acute myocardial infarction.[18,19] These studies suggest that hirudin is a potent anticoagulant that has minimal bleeding complications. It is a weak immunogen, has no effects on tissues or plasma proteins other than thrombin, has high bioavailability after a subcutaneous injection, and can be easily monitored using the prothrombin time.

TABLE 4.—*Hirudin and Its Analogues*

Hirudin Type	*Source*
Native hirudin	Isolated from the salivary glands of *Hirudo medicinalis*
Recombinant hirudin	Synthetic hirudin identical to native hirudin except that ^{63}Tyr is not sulfated (desulfatohirudin)
Hirulog	A derivative of hirudin in which 20 amino acids of the carboxy-terminus of the native molecule are coupled to phenylalanine-proline-arginine
Hirugen	A carboxyterminal analogue of hirudin

A disadvantage of hirudin is that there is no antidote currently available to reverse an accidental overdose.[18,19]

Another class of novel anticoagulant that is less well studied than LMW heparin or hirudin and its analogues is inhibitors to factor Xa. Two natural sources are the soft tick *(Ornithodoras moubata)* and the Mexican leech *(Haemanteria officinalis)*. Re-combinant products from each creature are being studied in animal models of arterial thrombosis. These agents are called tick anticoagulant peptide[22] and antistasin,[23] respectively.

Novel Antiplatelet Agents

Novel antiplatelet agents include those that inhibit platelet membrane receptors for fibrinogen (glycoprotein IIb-IIIa complex), von Willebrand factor (glycoprotein Ib), and the thromboxane A_2 receptor and thromboxane A_2 synthetase. The inhibition of these targets of activity would decrease platelet aggregation, adhesion, and activation, respectively. Inhibiting these platelet functions should be beneficial in the prophylaxis or treatment of arterial thrombosis. Major attention has focused on developing drugs to target the glycoprotein IIb-IIIa complex, including peptide inhibitors, and a monoclonal antibody to this receptor.[24] The glycoprotein IIb-IIIa complex is a member of a family of receptors known as the integrins; these receptors recognize the sequence arginine-glycine-aspartate (Arg-Gly-Asp) that represents the cell attachment regulation sequence present in certain adhesive proteins, such as fibrinogen.[25] Peptide inhibitors being developed are based on proteins isolated from various pit viper venoms.[26] For example, barbourin is a synthetic peptide based on a protein isolated from the venom of *Sistrurus m barbouri*, the southeastern pygmy rattlesnake (Figure 2).[27] Barbourin and other related peptides, called disintegrins, contain the Arg-Gly-Asp sequence and block adhesive functions of Arg-Gly-Asp-dependent integrins, including the platelet fibrinogen receptor.[28] These disintegrin peptides are being investigated in phase I and II clinical trials for the treatment of arterial thrombosis, especially acute myocardial infarction and angioplasty.

Another strategy for inhibiting platelet function involves developing a monoclonal antibody to the fibrinogen receptor. A chimeric (human-murine) monoclonal antibody to the glycoprotein IIb-IIIa complex is under phase III investigation for the prevention of arterial thrombosis.[24]

Less clinical information is available on the possible use of inhibitors to the glycoprotein Ib receptor, but given the importance of von Willebrand factor binding to platelet glycoprotein Ib (and glycoprotein IIb-IIIa) under conditions of high shear stress—similar to the flow conditions in a coronary artery—inhibitors of this adhesion receptor may prove to be highly effective antithrombotic agents.[29]

Another group of antiplatelet drugs target the platelet arachidonic acid metabolic pathway, especially the thromboxane A_2 pathway. One of the more promising agents in this group is ridogrel, a combined thromboxane synthetase inhibitor and thromboxane A_2 receptor inhibitor. This drug has been studied primarily in Europe with pilot studies done in patients undergoing angioplasty.[30]

Figure 2.—*Sistrurus m barbouri*, the southeastern pygmy rattlesnake, is the source of the antiplatelet peptide, barbourin. Venom from various pit vipers contains related antiplatelet agents. (This photograph was provided by John Tashjian.)

Fibrinolytic Agents

The last group of novel antithrombotic agents to be discussed is fibrinolytic agents, including tissue-plasminogen activator (t-PA) mutants and vampire bat-plasminogen activator. Recombinant t-PA is currently available for the treatment of venous thromboembolism and acute myocardial infarction; however, t-PA is not an ideal fibrinolytic agent in that it is not fibrin-specific and possesses a short half-life, rendering it less useful for bolus administration. To improve these functions of the t-PA molecule, the use of recombinant mutants is being investigated. Preliminary results with mutant t-PA preparations suggest that these drugs have enhanced fibrin specificity and a more prolonged half-life.[31] Clinical trials to establish the usefulness of mutant t-PA have not yet been reported.

A potentially new approach to fibrinolytic therapy is presented by the vampire bat (*Desmodus rotundus*, Figure 3). A potent plasminogen activator called vampire bat-plasminogen activator has been extracted and purified from the salivary secretions of this creature. Recombinant vampire bat-plasminogen activator is available for investigation. Results to date in animal models of thrombosis indicate that it shows superior fibrin specificity to t-PA, and when given by the intravenous bolus route, it has a substantially longer half-life.[32]

Summary

The prospects for more effective and safer antithrombotic therapy appear promising. I have presented only a portion of all novel antithrombotic agents currently under basic and clinical investigations. A discussion of additional new antithrombotic drugs is presented elsewhere.[33]

Questions and Answers

PHYSICIAN IN THE AUDIENCE: *How does the cost of LMW heparins compare with that of standard heparin?*

DR RODGERS: Low-molecular-weight heparins will cost more than standard heparin; however, the savings of using these drugs in the outpatient treatment of venous thrombosis should offset their expected higher cost.

Figure 3.—*Desmodus rotundus,* the vampire bat, is the source of a novel fibrinolytic agent that may be more fibrin-specific than currently available fibrinolytic agents. (This photograph was provided by Roger Caras.)

PA: *Does therapy with the antiplatelet monoclonal antibody result in secondary antibody production?*

Dr Rodgers: The original murine monoclonal antibody was immunogenic, but the chimeric monoclonal antibody under current investigation apparently does not induce an antibody response.

PA: *Can you address the paradox of why less bleeding is associated with more potent drugs and also comment on why there is no need for laboratory monitoring with LMW heparin?*

Dr Rodgers: It is thought that LMW heparin and standard heparin exhibit different effects on platelet function and vascular permeability. Low-molecular-weight heparin inhibits platelet function less than standard heparin, and unlike heparin, LMW heparin has no effect on vascular permeability. These distinctions may explain the hemorrhagic complications seen with standard heparin therapy.

With regard to why laboratory monitoring is not required for LMW heparin, there is a more predictable biologic response to these drugs. Low-molecular-weight heparins possess a higher bioavailability than standard heparin and are not bound to cells or plasma proteins so that when they are administered, a more uniform anticoagulant response occurs, permitting dosage based solely on body weight.

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Management of Necrotizing Pancreatitis

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A comprehensive management plan is presented for patients with severe acute pancreatitis. These patients may have pancreatic or peripancreatic necrosis or pancreatic fluid collections. Multiple organ failure often develops in patients with severe pancreatitis. We therefore recommend that all patients with acute pancreatitis be evaluated for pancreatic anatomy and function. If a patient is seriously ill, a computed tomographic (CT) scan with vascular enhancement should be done. Meanwhile, vigorous fluid replacement is necessary using Swan-Ganz monitoring. Patients with necrosis do not need surgical intervention unless the clinical course or CT scan-guided aspiration shows infection. The objective of an operation should be to remove all infected tissue and fluid. A preoperative CT scan with vascular enhancement should be used as a guide during the operation to ensure that all foci of infected necrosis or fluid are eliminated. We have found that open packing and irrigation with sodium oxychlorosene are helpful in patients with extensive necrosis or those who become infected early after the onset of symptoms. In all, 40% to 50% of patients treated by closed drainage will require reoperation because of incomplete debridement. Persistent sepsis is an indication for reoperation.

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About 80% of patients with acute pancreatitis have a mild form of the disease characterized by interstitial edema and often fat necrosis involving the pancreas and peripancreatic structures. Pancreatic and peripancreatic necrosis is rarely present and, if so, is limited to microscopic amounts. Local complications of necrosis, abscess or pseudocyst, or organ failure are absent. Most of these patients recover uneventfully after intravenous fluid replacement and the restriction of oral intake.

Patients with sterile or infected pancreatic or peripancreatic necrosis and those with sterile and infected pancreatic fluid collections have severe pancreatitis. Organ failure is frequently present. This report concerns the management of patients with severe pancreatitis.

In most patients, necrosis, when it occurs, develops within hours of the onset of symptoms, although there are a few patients in whom necrosis may develop as long as three to four days after symptoms begin. Necrosis of either the duct system or pancreatic parenchyma is the initiating event in most of the complications of acute pancreatitis[1,2] and occurs in the absence of bacteria.[3] As a result, about 10% of all patients with acute pancreatitis will have fluid collections due to the extravasation of fluid from the pancreatic ductal system. Another 10% with necrosis of more than 10% to 15% of the gland have a 40% to 70% chance of becoming infected.[4] Infection rarely occurs in the absence of pancreatic or peripancreatic necrosis. Consequently, pancreatic infections will develop in only 5% of all patients with acute pancreatitis, but 80% of all deaths from pancreatitis result from these infections. The other deaths are due, for the most part, to necrosis.[5,6] Much of the knowledge of the natural history of necrotizing pancreatitis is derived from the Ulm, Germany, group headed by Hans Beger.

The main factor that increases the likelihood of infection is the extent of pancreatic and peripancreatic necrosis. The more necrosis, the higher the incidence of infection. Infection can occur as early as two to three days after the onset of symptoms, but most cases occur later. The incidence of infection increases over the first three weeks, peaks during the third and fourth week, and then falls off rapidly. Whereas the incidence of infection is low the first week after symptoms begin, the mortality is in the range of 70% to 100%.[7] Each week thereafter, the mortality falls—to about 40% the second week, 27% the third week, and 13% the fourth week.[7,8]

The reasons for the high mortality associated with the early onset of infection are many. Patients infected early are physiologically sicker and have higher Ranson and APACHE [Acute Physiology and Chronic Health Evaluation] II signs of severity than those who become infected later.[9,10]* At an operation, the debridement of necrotic and peripancreatic tissue in those who become infected is more formidable not only because the patient is sicker, but because the operative procedure is technically more difficult. Debridement is often limited by the inability to distinguish viable from nonviable tissue. Frequently patent blood vessels traverse the necrotic areas in the pancreas and bleed during debridement. Fibrosis and granulation tissue do not begin to define and confine the areas

*See also the editorial by H. A. Reber, MD, and D. W. McFadden, MD, "Indications for Surgery in Necrotizing Pancreatitis," on pages 704-707.

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ABBREVIATIONS USED IN TEXT

APACHE II = Acute Physiology and Chronic Health Evaluation
CT = computed tomographic
UCD = University of California, Davis

of necrosis until the third week. Overall, patients infected early are more likely to require reoperation.

Unresolved Management Issues of Necrotizing Pancreatitis

Surgeons interested in this disease agree that when infection occurs, operative intervention is indicated. Surgeons disagree, however, as to whether patients with extensive sterile necrosis in whom there is a high probability of infection and in whom the mortality is high would benefit from a "preemptive operative strike," that is, removing all sterile necrosis before infection supervenes, as advocated by Rattner and co-workers.[6] They also disagree on whether the use of antibiotics will prevent or delay the occurrence of infections in patients with pancreatic or peripancreatic necrosis, as proposed by Bassi and colleagues.[11] Either outcome would be desirable. Few question the importance and necessity of vigorous fluid replacement in the resuscitation of patients with high Ranson or APACHE II scores and severe pancreatitis. The type of fluids and the goals of resuscitation, however, have not been defined.[5,12] The value of peritoneal lavage for 10 to 14 days—as opposed to 24 to 48 hours[13]—advocated by Ranson and Berman[14] is that it reduces the incidence of pancreatic and peripancreatic infection and mortality. This observation needs to be confirmed by others. The mechanism by which prolonged lavage might benefit a patient—by removing harmful substances from the abdominal cavity[15,16] or by providing improved fluid resuscitation[17]—is not known. There is also disagreement among surgeons as to how infected patients should best be managed—that is, open versus closed drainage or percutaneous versus operative drainage of infected fluid collections.[18,19]

University of California, Davis, Medical Center Approach

The approach of the University of California, Davis (UCD), Medical Center to patients with necrotizing pancreatitis has evolved from an experience with 90 patients (Figure 1). This is one of the world's largest experiences with necrotizing pancreatitis.

Basic Principles

The mortality of necrotizing pancreatitis can be reduced by using a comprehensive management plan. This plan includes the following:

- The rapid evaluation and assessment of the physiologic and anatomic derangements by the use of the APACHE II score and computed tomographic (CT) scan with vascular enhancement;
- The prompt institution of vigorous fluid resuscitation in which the cardiac index is maintained and monitored using Swan-Ganz techniques;
- Attempts to identify and document septic foci early by CT scan-guided aspiration for Gram's stain and culture; and
- Aggressive surgical debridement with open drainage in selected patients with extensive pancreatic and peripancreatic necrosis.

Physiologic Assessment of Severity

Most patients (75%) with severe pancreatitis presenting to the surgery service at UCD Medical Center are referred from other hospitals; therefore, the Ranson signs are not applicable for their assessment. (Ranson's signs are only applicable to patients during their first 48 hours of hospital stay and have not been validated for use days or weeks later at the time of hospital transfer.) We consider patients with more than two Ranson signs to be severely ill or to have the potential for a severe illness to develop. Only 28% of patients with pancreatic infections had severe pancreatitis at the initial hospital admission by the criteria of Ranson.[21] Ranson's signs are also inconvenient. Only five are available the day of admission, and the other six are calculated at 48 hours. We have found more useful the APACHE II classification of severity (Table 1),[10] which can be applied to patients coming to the intensive care unit from the emergency department and to those who are hospital transfers. The APACHE II is calculated the day of admission. The worst values obtained in a 24-hour period are used to calculate the severity of each sign or symptom on a scale of 1 to 4. The APACHE II also makes provisions for a patient's state of health at the time of illness—that is, a chronic health evaluation. Patients with an APACHE II of 7 or greater are severely ill or have the potential for a severe illness to develop. In our first 50 patients, we found the mean APACHE II score to be 33.6 for those who died and 14.9 for those who survived. There were no deaths in patients with an APACHE II score of 25 or less. There was only one survivor with an APACHE II score above 25.[5]

We also use the Ranson or APACHE II score to determine which patients are candidates for CT scan with

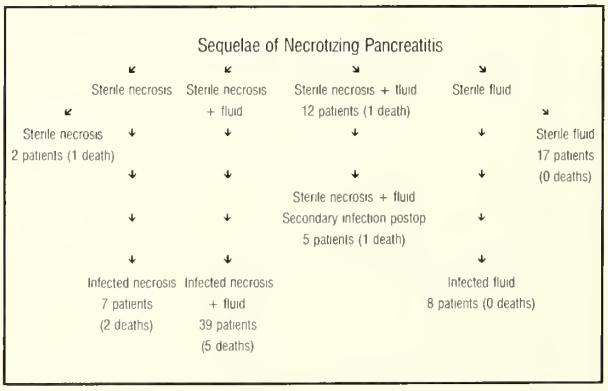

Figure 1.—The diagram outlines experience with 90 patients seen at the University of California, Davis, Medical Center with severe pancreatitis.

TABLE 1.—*APACHE II Severity of Disease Classification System*†

	High Abnormal Range, Points					*Low Abnormal Range, Points*			
Physiologic Variable	*+4*	*+3*	*+2*	*+1*	*0*	*+1*	*+2*	*+3*	*+4*
Temperature, °C	≥41	39-40.9		38.5-38.9	36-38.4	34-35.9	32-33.9	30-31.9	≤29.9
Mean arterial pressure, mm of mercury	≥160	130-159	110-129		70-109		50-69		≤49
Heart rate (ventricular response), beats per minute	≥180	140-179	110-139		70-109		55-69	40-54	≤39
Respiratory rate (nonventilated or ventilated), breaths per minute	≥50	35-49		25-34	12-24	10-11	6-9		≤5
Oxygenation: A-aDo_2 or Pao_2, mm of mercury									
Fio_2 ≥ 0.5 record A-aDo_2	≥500	350-499	200-349		<200				
Fio_2 < 0.5 record only Pao_2					Po_2 >70	Po_2 61-70		Po_2 55-60	Po_2 <55
Arterial pH	≥7.7	7.6-7.69		7.5-7.59	7.33-7.49		7.25-7.32	7.15-7.24	<7.15
Serum sodium, mmol/liter	≥180	160-179	155-159	150-154	130-149		120-129	111-119	≤110
Serum potassium, mmol/liter	≥7.0	6.0-6.9		5.5-5.9	3.5-5.4	3.0-3.4	2.5-2.9		<2.5
Serum creatinine, μmol/liter (mg/dl)‡	≥309 (≥3.5)	177-301 (2.0-3.4)	133-168 (1.5-1.9)		53-124 (0.6-1.4)		<53 (<0.6)		
Hematocrit	≥0.60		0.50-0.59	0.46-0.49	0.30-0.45		0.20-0.29		<0.20
Leukocyte count, × 10^9/liter	≥40		20-39.9	15-19.9	3-14.9		1-2.9		<1.0
Glasgow Coma Score§									
Total Acute Physiology Score (APS) II									
Serum bicarbonate, venous, mmol/liter¶	≥52	41-51.9		32-40.9	22-31.9		18-21.9	15-17.9	<15

A-aDo_2 = alveolar-arterial Po_2 difference, APACHE = Acute Physiology and Chronic Health Evaluation, Fio_2 = fraction of inspired oxygen, Pao_2 = partial pressure of arterial oxygen, Po_2 = partial oxygen pressure

*From Knaus et al.[10]

†Definitions: Organ insufficiency or immunocompromised state must have been evident before this hospital admission and conform to the following criteria: *liver*: biopsy-proven cirrhosis and documented portal hypertension, episodes of past upper gastrointestinal tract bleeding attributed to portal hypertension, or previous episodes of hepatic failure, encephalopathy, or coma; *cardiovascular*: New York Heart Association Class IV; *respiratory*: chronic, restrictive, obstructive, or vascular disease resulting in severe exercise restriction: unable to climb stairs or perform household duties; or documented chronic hypoxia, hypercapnia, secondary polycythemia, severe pulmonary hypertension (≥40 mm of mercury), or respirator dependence; *renal*: receiving dialysis; *immunocompromised*: the patient has received therapy that suppresses resistance to infection—immunosuppression, chemotherapy, irradiation, long-term or recent high doses of steroids, or has a disease that is sufficiently advanced to suppress resistance to infection, such as leukemia, lymphoma, or acquired immunodeficiency syndrome.

The APACHE II score is the sum of A + B + C:

A = APS points

B = age points: ≤44 yr, 0 points; 45 to 54 yr, 2 points; 55 to 64 yr, 3 points; 65 to 74 yr, 5 points; ≥75 yr, 6 points

C = Chronic Health points: If the patient has a history of severe organ system insufficiency or is immunocompromised, assign points as follows: for nonoperative or emergency postoperative patients, 5 points; for elective operative patients, 2 points.

‡Double-point score for acute renal failure.

§Score = 15 − actual Glasgow Coma Score.

‖Sum of the 12 individual variable points.

¶Not preferred; use if no arterial blood gas values.

vascular enhancement (Ranson: more than 2 signs of severity; APACHE II: 7 or above).

Anatomic Assessment of Severity

Although the Ranson and APACHE II scores are predictors of whether or not a patient survives, the CT scan with vascular enhancement is most useful as a predictor of those patients in whom the potential for infection exists. Between 40% and 70% of patients who have more than 30% necrosis of their pancreas will become infected.[4] Conversely, patients without pancreatic or peripancreatic necrosis will not become infected.

Those patients who have, on the basis of CT scan with vascular enhancement, 15% to 30% or more pancreatic necrosis, peripancreatic necrosis, or fluid collections in or around the pancreas are considered to have severe pancreatitis. A recent report by Foitzik and associates compared the effect of intravenous contrast medium on mortality in rats with exposure to pancreatitis of uniform severity and those in which no contrast was used.[22] The contrast was given within 24 hours of the pancreatitis being induced. If this report is confirmed, it would be advisable to delay CT scan with vascular enhancement until at least 24 hours after the onset of symptoms.

Fluid Resuscitation Therapy

Hemodynamic studies in humans have shown that there is a hyperdynamic cardiovascular state in patients with severe pancreatitis similar to that seen in patients with cirrhosis or septicemia. The exact mechanism whereby edematous pancreatitis evolves into necrotizing pancreatitis or perhaps begins de novo as necrotizing pancreatitis is not known.[23] Blood flow is known to be reduced to the pancreas during pancreatitis. In addition, patients are at risk of shock and the sequelae of shock and multiple organ failure as a result of a profound microvascular leak. Fluid is lost into interstitia, subcutaneous tissues, lungs, peritoneal cavity, and the pancreas, bowel, and retroperitoneum in severe pancreatitis. Pancreatic ascites and pulmonary effusion are common. The average positive fluid balance on the day of admission among our patients who died was 9.7 liters compared with 2.7 liters among survivors.[5] Patients with severe pancreatitis have diminished peripheral resistance and decreased intravascular volume. It is thought that trypsin released into surrounding tissues and the circulation triggers the complement cascade, kinins, prostaglandins, and eicosanoids, which has a profound effect on the integrity of the microvascular system.[12] To maintain circulation to the pan-

creas and other vital organs, we recommend a regimen of vigorous fluid resuscitation in patients with severe pancreatitis in whom the cardiac index is maximized to create a hyperdynamic circulation. Monitoring with a Swan-Ganz catheter is essential to achieve this goal. Special resuscitation regimens in animals using hypertonic saline-6% dextran 70 solutions produced marked improvement in cardiac contractility and pulmonary function over conventional resuscitation methods with electrolyte solution.[24] Schmidt and co-workers reported a decrease in mortality and in the incidence of pancreatic necrosis in rats using high-molecular-weight dextran 400 as the resuscitation solution.[25]

The use of furosemide to "maintain urinary output" in patients with severe pancreatitis is to be condemned. Organ hypoperfusion results, and multiple organ failure is the inevitable consequence. The hemodynamic phase of pancreatitis persists for four to six days when, if infection does not intervene, microvascular integrity returns and the patient's fluid requirements diminish.

Identifying Patients With Infection

Pancreatic necrosis and peripancreatic necrosis may cause leukocytosis, fever, and loss of microvascular integrity in the absence of infection. These manifestations of severe pancreatitis are difficult to distinguish from those of sepsis. Therefore, we use CT scan-guided aspiration to obtain Gram's stains and cultures in patients in whom there is any question of infection. This technique, described by Gerzof and associates,[26] is useful in patients in whom infection develops early after the onset of symptoms. We do not recommend operative intervention in patients with sterile necrosis early after the start of symptoms. Although this has been recommended by Rattner and colleagues,[6] their patients had a higher mortality than ours, 24% versus 14%. Of concern, in a substantial percentage of their patients, the sterile necrosis was converted to infected necrosis. Although their patients seemed to be less ill than ours by the APACHE II score, the comparison is not valid as our scores were obtained on admission to the UCD Medical Center's surgical intensive care unit and theirs on the day before operation.[6] Selected patients with sterile necrosis who remain ventilator-dependent or unable to eat after five to ten weeks require operative intervention.

The question of whether the use of antibiotics to prevent or delay infection is justified has not been completely settled. There is a high incidence of bacteremia during severe pancreatitis. Using imipenem in a multi-institutional study in Italy, Bassi and co-workers noted a reduction in the incidence of infection in patients receiving presumptive antibiotic therapy.[11] There was no decline in mortality, however. Previous studies from the 1970s that concluded the presumptive use of antibiotics to be unhelpful used antibiotics ineffective against enteric organisms, the ones most frequently found in necrotizing pancreatitis. The antibiotics were administered to an unselected group of patients with acute pancreatitis, most of whom had no necrosis.

Operative Management

Once infection is identified on the basis of clinical evidence of sepsis or the results of CT scan-guided aspiration, the infected pancreatic and peripancreatic necrotic tissue should undergo vigorous debridement (Figure 2). The preoperative CT scan with vascular enhancement is used to locate and remove all infected tissue and fluid.

We favor a bilateral subcostal incision, which provides access to the lesser sac and allows the hepatic and splenic flexures of the colon to be mobilized. If there is CT scan evidence of extension inferiorly into the small bowel mesentery, a separate incision into the mesentery below the colon is necessary. If there is extensive necrosis behind either colon, a counterincision is made in the flank for bringing out drain tubes and assisting in the debridement of the necrosis. Should necrotic colon be present, a proximal colostomy is done and the distal colon irrigated until clear. If there is duodenal necrosis, the pylorus is stapled closed and a gastrojejunostomy performed. All

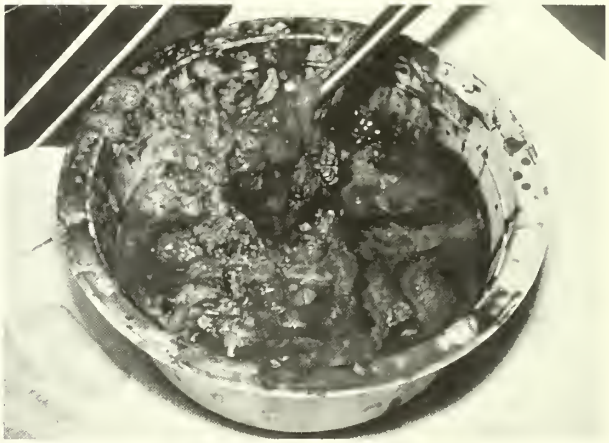

Figure 2.—Typical pancreatic and peripancreatic necrotic tissue was recovered at a necrosectomy.

necrotic tissue is weighed, and all the fluid removed is measured. Gram's stain and cultures are done for aerobic, anaerobic, and fungal organisms. After the debridement is completed, a decision is made as to whether to pack the surgical wound closed or open. The decision to pack open is influenced by the following: A large amount of necrotic pancreatic and peripancreatic tissue (more than 100 grams) is removed with the initial debridement; a preoperative CT scan shows more than 50% necrosis of the gland or extensive peripancreatic necrosis beneath the colon; and viable tissue is poorly delineated from nonviable tissue at the operation, which is usually seen in patients in whom infection intervened within the first several weeks after their symptoms began.

Drainage and Irrigation

Whether the drainage is open or closed, triple-lumen Davol drains are used for irrigation with sodium oxychlorosene (Clorpactin) solution. Initially we irrigate at 250 ml per hour per drain. Dependent drainage is used, with #40 silicone chest tubes brought out beneath the

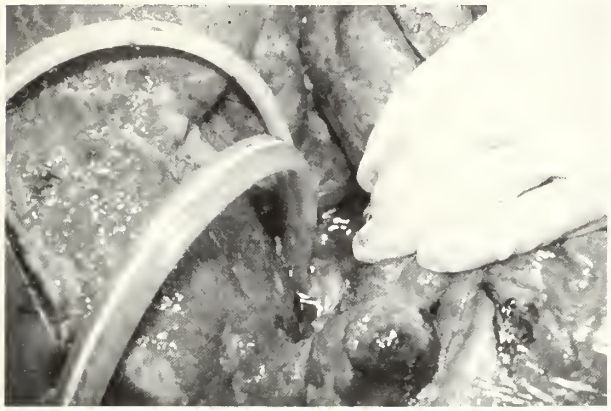

Figure 3.—Triple-lumen Davol drains are sutured to the skin at the edge of the incision for irrigation purposes.

colon in the flank. Suction is not used on the Davol drains because of bleeding complications that on two occasions necessitated a trip to the operating room for control.

At open drainage after placing the drains (Figure 3), the lesser sac is packed open with Kerlix rolls (Figure 4). There is no need to use Xeroform or Adaptic gauze to protect the bowel if irrigation is used. A space is thus created between the stomach and transverse mesocolon and colon that allows ready access to the anterior surface of the pancreas by simply removing the Kerlix rolls.

After the initial debridement, it is important to return on a regular basis every two to three days until all the infected necrotic tissue is debrided. After each debridement, a CT scan is done to determine if any pockets of infected necrosis remain. This process is repeated every two to three days until the abdomen is clean as observed at operation and by CT scan with vascular enhancement. The combination of infection and activated pancreatic enzymes may cause additional necrosis between debridement procedures.

If a patient has been treated by the closed or open technique and continues to have sepsis or does not improve, reoperation for what are inevitably pockets of undrained infected necrosis or fluid is mandatory. Frequently the major pancreatic duct is disrupted in the body of the pancreas so that the viable pancreatic tail continues to secrete pancreatic juice, creating a pancreatic fistula. The amylase levels in drain fluid should be measured, and if the volume of fluid and the amylase concentration are high, the drains should not be advanced. Some pancreatic fistulas will close as long as 8 to 12 months after they start.

Combined Therapy

We work closely with radiologists and often call on them to either drain isolated pockets of infected fluid as observed on CT scan or place a catheter into a collection. The catheter can also be used as an operative guide to locate pockets of infected necrosis in difficult-to-reach areas in the retroperitoneum. The percutaneous drainage of areas of infected necrosis, as a primary therapy, is an exercise in futility.[6]

Pancreatic Abscesses

Patients may develop a pancreatic abscess, which is a circumscribed intra-abdominal collection of pus containing little or no pancreatic necrosis. The abscess can best be drained operatively, although percutaneous drainage can be tried initially if a patient is a poor operative risk.

Fluid Collections

Large fluid collections can occur early in the course of acute pancreatitis, within days or weeks of the onset of symptoms following disruption of the main pancreatic duct or one of its branches. Usually there is some element of proximal ductal obstruction that leads to ductal hypertension and promotes the extravasation of pancreatic juice from the site of duct discontinuity. These fluid collections, unlike a pseudocyst, lack a wall of granulation or fibrous tissue. More than 50% of these collections will disappear spontaneously. Therefore, aspirating them before four to six weeks is meddlesome and unnecessary.

Our results in 90 patients observed from 1982 to mid-1992 show that patients with necrosis with or without associated fluid—as determined at the time of operative intervention—are at high risk of dying. Patients with fluid

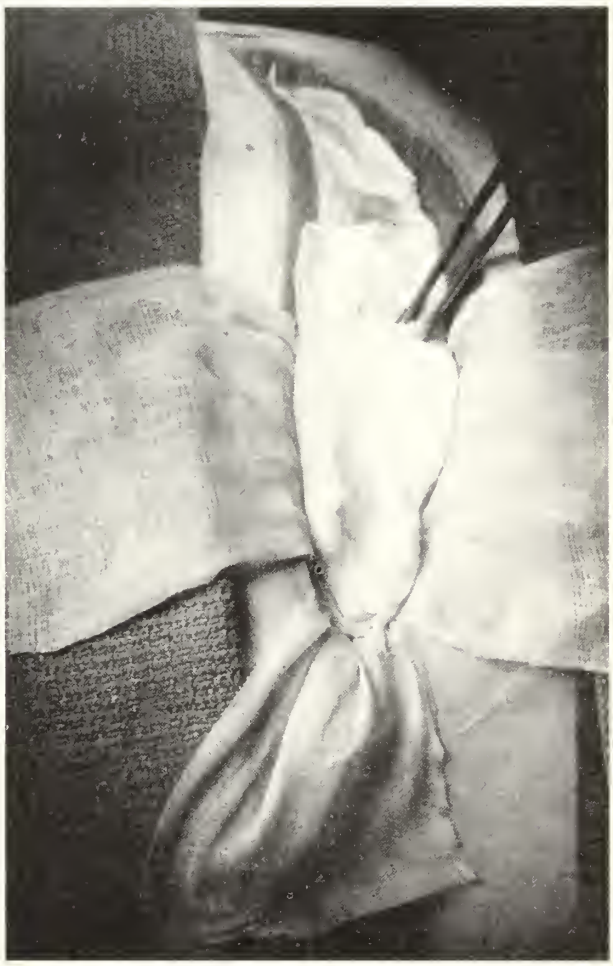

Figure 4.—The stomach is separated from the transverse colon and its mesocolon by Kerlix packing.

collections in the absence of necrosis, whether sterile or infected, all did well.

In summary, close adherence to the methods of care described herein has resulted in the mortality of necrotizing pancreatitis remaining at about 15%.

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Epitomes

Important Advances in Clinical Medicine

General Surgery

The Council on Scientific Affairs of the California Medical Association presents the following inventory of items of progress in general surgery. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome, and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, researchers, and scholars to stay abreast of these items of progress in general surgery that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on General Surgery of the California Medical Association, and the summaries were prepared under its direction.

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Innovative Treatment of Deep Venous Disease

ALTHOUGH VASCULAR SURGERY involving the arterial system has improved, the management of venous disease is still an area for investigation and innovative treatment. The classic management of deep venous insufficiency, which is the primary challenge for surgeons, involves stripping incompetent superficial veins, skin grafting stasis ulceration, and placing a patient on permanent elastic support. This is successful in more than 90% of cases. How to treat the other 5% to 10% of patients is the challenge.

The clinical manifestations of deep venous disease have two causes: Obstructed venous outflow from the lower extremities results in venous claudication, a deep bursting sensation from exercise; and deep venous insufficiency due to valvular incompetence results in stasis dermatitis and venous stasis ulcers.

When the obstruction is unilateral, venous decompression can be achieved using a cross-femoral autogenous saphenous vein or externally supported prosthetic grafts. When the process is bilateral or vena cava obstruction exists, the problem is more challenging. Femoral-to-atrial bypass, as well as femoral-to-superior vena cava bypass, offers possible solutions, but requires permanent anticoagulation and temporary adjuncts, such as femoral arteriovenous fistulas, to ensure initial patency.

Deep venous insufficiency can be managed with elastic support. When a patient cannot tolerate elastic compression and the process progresses, some form of surgical treatment is required. When ulceration is chronic, direct skin grafting of the ulcer usually is of no permanent benefit. The adequate treatment of ulcers requires wide excision of the area of scarring down to fascia before the split-thickness skin graft is applied. When pigmentation and scarring are extensive and circumferential, ulcer excision and grafting are best followed by subfascial excision of incompetent veins communicating with the deep system that feeds the process (Linton procedure). Deep vein insufficiency, at this point, can then usually be controlled successfully with knee-length elastic stockings (30 to 40 mm gradient).

When a patient is unable to tolerate elastic support or skin problems recur, venous valvular reconstruction can be used. A descending phlebogram is necessary to verify both total valvular incompetency and patency of the deep venous system. The axillary vein, when harvested, can provide one or two competent valves, which are optimally placed in the popliteal position. This procedure has been associated with immediate good results and looks promising for the long term, with 75% of veins remaining patent and functional after 18 months. These patients require permanent anticoagulation to prevent a recurrence of the thrombotic process. Alternative techniques, which so far have been less successful, include the repair of incompetent valves using angioscopy or deep vein ligation combined with a subfascially placed competent saphenous vein bypass.

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Current Role for Radiation Therapy in Ductal Carcinoma in Situ

OUR UNDERSTANDING OF ductal carcinoma in situ and its management has changed substantially since the term was first used in 1960. We now know that ductal carcinoma in situ, like lobular carcinoma in situ, arises from

the terminal ductolobular unit, and invasive cancer will develop over ten years in 30% to 50% of patients. Until recently, mastectomy was considered the most appropriate treatment of this malignant lesion. The case for whole-breast treatment was based on such issues as a 41% incidence of multifocality (two lesions in the same quadrant), a 30% incidence of multicentricity (two lesions in two different quadrants), a 20% incidence of occult invasive tumor, and a recurrence rate after wide excision only of about 25%.

As in the treatment of invasive cancer, however, the trend has been toward whole-breast radiation therapy as opposed to mastectomy. Because breast conservation is now accepted for invasive cancer, some have argued that a less invasive lesion, ductal carcinoma in situ, should not be treated more aggressively than its invasive counterpart. Others have questioned the efficacy of radiation treatment of ductal carcinoma in situ on the basis that its slower growth rate may make it less responsive to irradiation. A combination of lumpectomy plus whole-breast irradiation apparently yields the best results.

Most patients with ductal carcinoma in situ present with mammographic microcalcifications. Most of these patients are best treated with local excision followed by six weeks of radiation therapy. There are patients, however, who require either less or more aggressive treatment than this standard regimen. For patients presenting with a small cluster of microcalcifications that is completely excised and found to be noncomedo type carcinoma in situ, it is likely that excision alone will offer a low recurrence rate comparable to excision plus radiation therapy.

At the other end of the spectrum, factors favoring mastectomy for this neoplasm include its presenting as a palpable mass greater than 2 cm and extensive radiographic (diffuse microcalcifications) or pathologic breast involvement. Comedo versus noncomedo type may, along with other factors, influence the choice for mastectomy. Estrogen and progesterone receptor status currently does not influence the choice of therapy.

The controversy over the role of axillary dissection for this disease has been largely resolved over the past few years. Because ductal carcinoma in situ by definition is contained within the duct, there is theoretically no chance for spread through lymphatics or the vascular system, as these structures are outside of the ductal system in the breast parenchyma. Large series on the results of lymph node dissections for ductal carcinoma in situ show an incidence of positivity of 1% to 3%. For these reasons, axillary dissection is seldom done unless there is evidence of microinvasion.

The goal of therapy for this disorder is to prevent recurrent disease and increase the chances for long-term survival. If cancer recurs after a diagnosis of ductal carcinoma in situ, it will be invasive disease in half of patients and recurrent disease in the other half. The recurrent disease will most often be in the same quadrant as the initial focus. It now seems that excising the focus of ductal carcinoma in situ, without axillary dissection, followed by radiation therapy offers the best chance of achieving both of the treatment goals. A current National Adjuvant Breast and Bowel Project trial is exploring the possible role of tamoxifen citrate in the treatment of this neoplasm.

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Nonoperative Management of Blunt Liver Injuries

LAPAROTOMY IN PATIENTS with liver injuries that are not bleeding is not therapeutic and may delay the treatment of associated injuries. Most liver injuries are not bleeding at the time of surgical exploration. These observations and a large experience with the nonoperative management of abdominal trauma in children have stimulated the development of a strategy for the nonoperative management of blunt liver injuries in adults. About 20% of patients with blunt liver injuries are candidates for nonoperative therapy; the approach succeeds in 90%.

Nonoperative management of blunt solid organ trauma is based on a diagnostic strategy that can identify and classify specific injuries. In modern practice, computed tomography (CT) is most often used for this purpose because it is noninvasive and provides specific anatomic information. Patients with hemodynamic instability are not candidates for CT; peritoneal lavage is used for diagnosis, and the presence of hemoperitoneum is an indication for laparotomy. The limitations of CT also must be considered. The test is relatively insensitive for injuries of hollow organs (the gastrointestinal tract) and the diaphragm, it is expensive, some degree of interpretation is needed, and correlation with the degrees of organ injury found at laparotomy has been imperfect at best. Subcapsular hematomas and parenchymal lacerations and hematomas are typical lesions treated nonoperatively.

Patients must be under the care of an experienced trauma surgeon. Vital signs must be stable after the initial resuscitation, and diffuse peritoneal signs must be absent. Computed tomography using intravenous and oral contrast media should be done immediately and interpreted by an experienced radiologist to exclude other abdominal injuries requiring an operation. The patient must be monitored in an intensive care unit with frequent evaluations of vital signs, physical findings, and laboratory tests. The need for laparotomy is determined by the overall clinical condition, not the radiographic appearance of the liver. Access to an operating room must be available at all times. Continued bleeding is an indication for immediate laparotomy. Patients must not be allowed to bleed to the point of hemodynamic instability or coagulopathy. Exploration is generally advised if transfusion requirements exceed one to two units of packed red blood cells, unless bleeding is clearly due to an extra-abdominal source. A

follow-up CT scan in the first two to seven days is useful to show progression or resolution of the hepatic lesion. If logistic difficulties in adhering to these principles are anticipated, then an exploratory procedure should be done at the outset.

Hemobilia and bile leakage are two rare complications of nonoperative therapy. In collected series, virtually no deaths attributable to the hepatic injuries have occurred, underscoring the importance of careful patient selection and close monitoring.

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Repair and Follow-up of Leg Arteries With Vein Grafts

About 80% of leg arterial reconstructions are done for ischemic rest pain, pedal ulceration, or gangrene. The best conduit for infrainguinal revascularization is an autogenous vein. Unfortunately, vein grafts can fail with resultant ischemic pain or additional tissue loss.

Options for patients with thrombosed infrainguinal vein grafts are all unsatisfactory, but treatment must be undertaken. Thrombolysis is expensive and carries a serious complication rate of 15%. It is initially successful in restoring graft patency in only about 60% of thrombosed grafts. Adjunctive graft revision is also often required. Less than half of grafts successfully lysed remain patent at one year. Replacing a thrombosed vein graft with a prosthetic graft yields similarly poor patency rates. A new autogenous vein graft is the best option, but such operations are technically difficult. They often require harvesting arm veins or lesser saphenous veins, operative sites may be scarred, and one or more venovenostomies may need to be done to achieve a conduit of adequate length. Obviously, the prevention of vein graft thrombosis is desirable.

Nearly 80% of vein graft failures result from a stenosis in the graft itself or its inflow and outflow arteries. Graft lesions typically occur near the proximal or distal anastomoses or at valve sites and most frequently develop during the first 24 months after implantation. Native artery lesions usually occur later.

Clinical follow-up alone is inadequate for identifying grafts at risk for near-term thrombosis. Many grafts fail without premonitory changes in the pulse or preceding symptoms. Interestingly, vein grafts fail just as frequently in limbs with stable, serially obtained, ankle:brachial systolic blood pressure indices as in limbs with deteriorating values.

The propensity for vein grafts to fail unpredictably is a complication that can be largely avoided. A program of vascular laboratory surveillance using duplex ultrasonography can reliably identify stenoses in vein grafts or inflow and outflow vessels. Vein grafts monitored in this way and appropriately revised have a substantially improved overall patency rate compared with grafts observed and revised based on recurrent symptoms or deteriorating physical findings or blood pressure differentials. Grafts revised before thrombosis occurs appear to have late patency rates equal to those of vein grafts that never develop a detectable stenosis and never require revision. These patency rates exceed 80% at five years.

For in situ vein grafts, a peak systolic velocity of less than 45 cm per second in the distal portion of a 3- to 4-mm graft is considered a marker for short-term graft failure. Such grafts typically have a stenosis identified by angiography. Unfortunately, this velocity value is not absolute as many vein grafts, both in situ and reversed, will have a greater than 50% stenosis despite peak systolic velocities of 45 cm or greater per second. Conversely, as many as 20% of reverse grafts may have a velocity of less than 45 cm per second in the distal portion of the graft with no detectable stenosis. As focal stenosis appears to precede most graft failures, screening for stenosis is becoming the standard method of vein-graft duplex surveillance. A peak systolic velocity of two or more times the peak systolic velocity in the immediately preceding portion of the graft, or 200 cm or more per second, reliably indicates greater than 50% stenosis at the site of the high velocity.

Although a few vein grafts may remain patent for prolonged periods despite high-grade lesions, failure is expected. High-grade vein graft stenoses should be repaired when identified in appropriate patients. Given the propensity for vein grafts to fail early, a program of graft surveillance using duplex ultrasonography every three to six months in the first two years postoperatively is prudent. If the graft remains patent without the need for revision during this time, surveillance can probably be extended to yearly.

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Current Status of Pancreas Transplantation

Advances in immunosuppression, refinements in surgical techniques, and developing methods to assess the presence of rejection have led to a resurrection of pancreas transplantation in the past decade. Current graft survival rates are comparable to the other solid organ transplants. Recent reports have documented pancreas graft survival rates as high as 92% at 15-month follow-up. Thus, pan-

creas transplantation should be considered a therapeutic option in appropriately selected patients with insulin-dependent diabetes mellitus.

Recent data document a 70% to 75% overall one-year graft survival. Centers that do larger volumes have reported more than an 80% one-year pancreas graft survival. The results of long-term follow-up are also encouraging for patients who have graft survival at the end of a year. There is more than a 70% likelihood that they will have a functioning pancreas graft after five years. Mortality in patients with combined kidney-pancreas transplants is no higher than for kidney transplants alone in patients with diabetes, with most centers reporting more than 95% one-year patient survival rates.

The effects of pancreas transplantation on glucose metabolism have been well established. Normoglycemia is achieved without the need for exogenous insulin. In addition, oral or intravenous glucose tolerance tests, 24-hour glucose profiles, and hemoglobin A_{1c} levels are all normal after successful transplantation. This may translate into a substantial improvement in quality of life, especially for those patients with brittle diabetes and widely fluctuating serum glucose levels. Several studies show improved quality of life after pancreas transplantation. Patients feel healthier, are more independent, return to employment more frequently, and prefer long-term immunosuppression to insulin. Morbidity after pancreas transplantation during the initial three to six months is higher than after kidney transplantation alone. Patients will have more rejection episodes and a higher incidence of infections, but at one year, there is no difference in patient survival between patients with a pancreas transplant and those with a kidney transplant only.

Increasing evidence has demonstrated a beneficial effect of pancreas transplantation on the progression of the secondary complications of diabetes. Normoglycemia after pancreas transplantation prevents the recurrence of diabetic nephropathy in a transplanted kidney. Diabetic neuropathy also appears to be ameliorated after transplantation. Motor and sensory nerve conduction studies show substantial improvement after transplantation. The incidence of diabetic gastroparesis and enteropathy lessens. The effect of pancreas transplantation on diabetic retinopathy is less clear. Patients with successful pancreas transplantation may continue to have progression of retinopathy for 24 months after the procedure, but the process may stabilize after this period.

Most patients being evaluated for pancreas transplantation have advanced diabetic nephropathy and will receive a kidney transplant. Because these patients will have long-term immunosuppression, doing pancreas transplantation as well adds only the extra surgical risk. A successful outcome would mean normoglycemia with an improvement in quality of life and a possible beneficial effect on diabetic complications.

Other diabetic patients who might benefit from pancreas transplantation are those with difficult, brittle metabolic control but with normal renal function. These patients have no clinically serious nephropathy or have previously received a kidney transplant. The risks and benefits of surgery and immunosuppression must be individually assessed and contrasted to their problems with diabetes. Pancreas transplantation has been successful in this patient population, with a one-year graft survival rate of 80% if HLA matching is optimal. There is limited follow-up after solitary pancreas transplantation. Initial studies show that morbidity is no different from that after a kidney transplant; mortality is less than 5% at one year.

We should see further progress in the field of pancreas transplantation when it is applied to a wider spectrum of patients with diabetes.

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Laparoscopic Biliary Operation

SINCE THE FIRST planned cholecystectomy was done in 1881, there has been little change in the surgical treatment of symptomatic cholelithiasis. Cholecystectomy has always been considered a major operation but a relatively safe one. Reports from centers around the world are now showing that once surgeons have gained adequate experience, laparoscopic cholecystectomy can be done as safely as open cholecystectomy. In fact, reports in critically ill patients show laparoscopic procedures to be safer than "open" procedures. This led a National Institutes of Health consensus development panel to conclude that laparoscopic cholecystectomy is the treatment of choice for patients with symptomatic cholelithiasis.

Previous abdominal operations, acute cholecystitis, pancreatitis, morbid obesity, and common bile duct calculi are no longer thought to be contraindications to the laparoscopic approach. Its use in early pregnancy is still controversial. Enterotomies, bleeding bile leak, bile duct injuries, and conversion rates are higher when these problems complicate cholecystectomy. Complications occur in about 6% of patients, and conversion rates range from 2% to 10%.

Routine versus selective intraoperative cholangiography has been debated and remains controversial. Proponents argue that laparoscopic cholecystectomy is different from open surgery, and routine intraoperative cholangiography should be done to identify common duct calculi and decrease common bile duct injuries, or at least to identify the injuries at the time of the procedure. Preoperative endoscopic retrograde cholangiopancreatography (ERCP) has been advocated for patients suspected of having common duct calculi, but laparoscopic techniques of transcystic choledochoscopy, transcystic ampullary bal-

loon dilation, transcystic sphincterotomy, and laparoscopic choledochotomy have been introduced to retrieve common duct calculi during surgery when identified on intraoperative cholangiography. These techniques allow patients to be treated in one session and obviate the need for preoperative ERCP. Postoperative ERCP is an option in some patients. Local experience and skill remain the determining factors in deciding which approach to take.

Most agree that patients with asymptomatic cholelithiasis should not undergo cholecystectomy except some patients with diabetes mellitus and organ transplantation. Those who have biliary pain but no demonstrable calculi may have diagnostic tests such as duodenal drainage for pigment or cholesterol crystals or cholecystokinin-stimulated nuclear biliary scans. When gallbladder emptying is abnormal, 70% of patients improve with cholecystectomy.

Several cases of laparoscopic biliary bypass for malignant bile duct obstructions, excision of a choledochal cyst with hepaticojejunostomy, and even a laparoscopic Whipple procedure have been presented at national surgical meetings. In the future, most procedures involving the biliary tract may be done laparoscopically.

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Minimal-Access Versus Open Herniorrhaphy

THE ACCEPTANCE OF laparoscopic cholecystectomy has heralded the application of minimal-access surgery for a variety of other surgical problems. Minimal-access or "closed" herniorrhaphy has been proposed as a procedure that may decrease recurrences and speed the return to normal activity. Nearly 700,000 inguinal hernias are repaired each year; the recurrence rate is generally reported to be 8% to 15%. If closed herniorrhaphy lives up to its proponents' claims, then individual and societal gain could be great. Minimal-access herniorrhaphy, however, is as much as 135% more expensive than open procedures, requires general anesthesia, and has the potential for serious complications. Therefore, the results of this procedure must be closely scrutinized and compared with the gold standard of an open technique.

Most open primary herniorrhaphies are done on an outpatient basis with local anesthesia and predictable results. Morbidity is related to wound infection, ischemic orchitis, testicular atrophy, pubic tubercle parosteitis, hypesthesia, and paresthesia. The overall rate of most of these complications is 1% to 2%. This figure may double when recurrent hernias are repaired. The main disadvantage of the open technique is the recuperative disability, which ranges from two to six weeks, and the recurrence rate. Despite superb results from dedicated hernia surgeons, the literature reflects a continuing high recurrence rate.

Both the Shouldice and Lichtenstein repairs are generally accepted as standards for open herniorrhaphy. Both repairs are usually done under local anesthesia. With the Shouldice repair, the posterior inguinal wall is reconstructed and strengthened with four continuous sutures and without prosthetic material. Recurrence rates range between 0.45% and 2.7% in studies where patients are observed for 6 to 23 years. There appears to be a learning curve in perfecting the intricacies of this procedure. Of concern is the 7.2% recurrence rate when the Shouldice was used for recurrent herniorrhaphy.

The Lichtenstein repair uses a nonabsorbable polypropylene mesh to provide a tension-free repair of the posterior inguinal wall. The recurrence rate over six years is 0.13% to 1.6%. Infections or mesh rejections are rare. This repair may not be as difficult as other methods.

The attractiveness of minimal-access herniorrhaphy is not that it is minimally invasive; it is more invasive than open repair. Rather, there is superior visualization of the posterior inguinal anatomy to allow a tension-free mesh repair. Moreover, this repair is buttressed by the normally existing intra-abdominal pressure and does not require a long inguinal incision. Proponents of this technique cite the potential for reducing recurrences and minimal disability, with many patients resuming normal activity within 48 hours. Closed herniorrhaphy exposes patients to unique risks, however. These are gas embolism and trocar injury to a viscus and risks associated with intra-abdominal procedures. Moreover, it is not known if the mesh used for the repair or the potential devascularization of the peritoneal flap will cause an increase in the incidence of fistulae or adhesions with subsequent bowel obstruction. On the other hand, closed herniorrhaphy may actually decrease the incidence of complications of ischemic orchitis, testicular atrophy, wound infection, and nerve entrapment or hypesthesias.

Minimal-access herniorrhaphy is a technique in evolution. Both transabdominal and extraperitoneal approaches have been described, but all methods use prosthetics. Because of the multiple techniques, few patients, and short follow-ups, all results should be considered preliminary. Recurrence rates over 6 to 11 months are in the range of 0% to 3.2%. Complications can include epigastric artery lacerations, transient testicular pain, hematoma, trocar incisional hernia, groin pain and hematoma, and wound infection.

Short-term recurrence rates, recuperative time, and complications of closed herniorrhaphy are not currently superior to those of open procedures. To be fair, these early results represent the initial experience and can be expected to improve with refinements in technique. Without a clear superiority, it will be difficult to recommend a closed procedure for primary hernia repair. Closed repair may be ad-

vantageous for bilateral or recurrent herniorrhaphy. The exact role of minimal-access or closed herniorrhaphy remains to be defined by randomized prospective trials.

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Treatment of Superficial Venous Insufficiency of the Legs

VENOUS DISORDERS are among the most common conditions seen and treated by medical practitioners, and duplex and color ultrasound examinations have vastly simplified clinical venous investigations. High-resolution ultrasonography is expanding the knowledge of the anatomic structure of telangiectasias and cutaneous venous blemishes, which is allowing more effective treatment by precise sclerotherapy. Cutaneous blemishes and telangiectasias do not require noninvasive evaluation.

Success in treating venous insufficiency depends on the realization that eliminating nonworking venous segments is crucial. Thus, routine saphenous stripping has been replaced by the limited removal of precisely defined incompetent segments. Often this is done by clever saphenous inversion techniques. To this is added the removal of varicose clusters with stab avulsion. Developments in instrumentation now allow the removal of varicosities through 1- and 2-mm incisions placed in skin lines. This improves the results of varicectomy while cutting its cost through avoiding the use of surgical facilities, general anesthesia, and recovery rooms.

Advances in ablating symptomatic telangiectatic blemishes by sclerotherapy now supplement minor surgical techniques. Although not recognized by third-party insurance carriers, cutaneous telangiectatic blemishes are frequently symptomatic. Success in treating these lesions has been achieved in this country by diluting available sclerotherapeutic agents. The most common of these agents is administered in 0.1% to 0.25% concentration rather than as supplied as a 3% solution. In other countries, the almost uniform use of polidocanol (not approved for use in the United States) in sclerotherapy has led to clinical trials that will eventually allow its use here.

The role of activated leukocytes in producing lipodermatosclerosis in limbs called postphlebitic in the past is being investigated. As these investigations go on, treatment with available pharmacologic medications is ameliorating severe problems of venous insufficiency. Pentoxifylline, in particular, has been found in a multi-institutional prospective trial to enhance the healing of venous ulcerations.

There is no doubt that other options for treatment will be explored. In addition, we can anticipate the application of evolving laser therapy to extend treatment to depths of 1 to 22 mm. This can now be done without producing pain or cutaneous changes.

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Video-Assisted Surgical Techniques in Infants and Children

ALL SURGICAL SPECIALTIES have experienced rapid growth in video-assisted techniques in the past five years, and pediatric surgery is no exception. The growing role of video technology in surgical procedures is related to the availability of equipment that provides an adequate magnified image through small incisions or endoscopes. Cameras smaller than the human palm, linked with telescopes that employ the Hopkins rod lens technology, deliver an image that is true color, magnified, and well focused.

Rigid and flexible endoscopes have been used for a number of diagnostic and therapeutic purposes in children. The application and success of these techniques have been limited in smaller children and infants by poor-quality images. Telescopes and flexible endoscopes now employ a series of lenses or fiber-optic cables to deliver a satisfactory image to a high-quality television monitor even in small instruments.

Diagnostic endoscopic procedures include the assessment of vocal cord function and the presence of tracheomalacia, vascular rings, tracheoesophageal fistulae, gastroesophageal reflux, and many other conditions of the airway and upper and lower gastrointestinal tracts. Video-assisted techniques permit still and video recordings of findings and documentation for comparison of patients' progress on reexaminations and assist with therapeutic interventions.

Video-assisted exploration of the chest and mediastinum has both diagnostic and therapeutic benefits for children. Patients must be anesthetized and supported by positive pressure ventilation through a double-lumen endotracheal tube. The anesthesiologist may then collapse the lung on the side to be examined to allow visualization without injuring the lung. Thoracoscopic technique is limited to children weighing 25 kg and more because of the need for a double-lumen endotracheal tube. In many cases several incisions equivalent to chest tube sites are substituted for the morbidity of a formal thoracotomy.

Cholecystectomy is much less commonly indicated in children and is usually associated with liver disease or hereditary anemia, such as sickle cell disease, thalassemia, or spherocytosis. These children may be treated by video-assisted techniques similar to those in adults. A direct fascial cut-down technique is used in a 10-mm periumbilical incision to place the camera port and to insufflate the abdomen using carbon dioxide. The telescope is then introduced and an additional 10-mm port

and two 5-mm ports are introduced to allow safe dissection and removal of the gallbladder.

Advanced therapeutic procedures require pediatric surgeons to have additional experience and training. These procedures have included Nissen fundoplication, appendectomy, splenectomy, resection of pelvic or ovarian malignant tumors, the management of high undescended testicles, and many other diagnostic procedures.

The indications for doing these procedures would include all of the factors usually considered for recommending an open procedure. Complicating factors that would contraindicate using a video-assisted technique include extensive previous surgical procedures, severe hepatomegaly or splenomegaly, or portal hypertension. The video-assisted technique may be particularly suitable for patients with compromised pulmonary function or impaired wound healing (chemotherapy, malnutrition), but these patients should still meet the standard indications for surgery that have been used to select patients for open procedures.

The complications would also be similar to those for open procedures. Unique considerations in laparoscopy would include unintentional injury to viscera from cautery and tension pneumothorax. Electrocautery in a closed abdomen may result in the transmission of energy from the intended site and requires particular care on the part of the surgeon.

At present only a small percentage of video-assisted procedures are being done in children. In the past year the types of procedures considered and the number of surgeons involved have expanded rapidly. With increasing use, we can expect these techniques to be further refined.

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Advances in the Screening and Staging of Colon and Rectal Cancers

OUR UNDERSTANDING OF the management of colon and rectal cancers has evolved dramatically in the past five years. There is an increased understanding of the natural history of these diseases as reflected in our staging and screening technologies.

The traditional Dukes' staging system is inadequate to evaluate colon and rectal cancers, and the use of tumor-node-metastasis staging has gained wide acceptance at most cancer centers. Tumor-node-metastasis staging is used because the depth of tumor penetration, the extent of lymph node involvement, and the presence of distant metastases best characterize patients' prognosis. In addition, this system is useful in more precisely comparing various surgical experiences and reports. Preoperative staging is being used only when findings would influence therapeutic alternatives. As a result, modalities that are now recognized as being helpful in preoperative staging—transrectal ultrasonography, flow cytometry, and computed tomography—are used sparingly.

Colon cancer is moving to the right. This is a result of not only an increase in the incidence of right-sided colon cancer, but also a decrease in the incidence of left-sided colon cancer. The same disease cannot be increasing and decreasing in incidence at the same time; therefore, it is now clear that right-sided colon cancer is a different disease from left-sided colon cancer. These diseases are different in their morphologic presentation, incidence, prognosis, and biologic markers. In evaluating various therapeutic options, the differences in these tumors must be recognized.

Controversy remains about the value of screening for colon and rectal cancers. Recent publications, however, strongly suggest that screening for occult blood in the stool is cost-effective and indeed prolongs the survival of patients in whom colon and rectal cancers subsequently develop. Prolonged follow-up has been necessary to show this advantage.

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Progress in Preventing Amputation in Leg Ischemia

PERIPHERAL VASCULAR SURGERY is succeeding in preventing stroke through carotid endarterectomy, extending the length of comfortable life through aortic aneurysm resection, and is becoming increasingly successful in preventing lower extremity amputation. For example, one group rejected only 11 of 564 limbs (1.9%) requiring distal revascularization. These were limbs with advanced ischemia or contractures considered nonsalvagable. This was a category that ten years ago ranged from 5% to 15% of patients with critical limb ischemia.

Increasing experience in harvesting autogenous veins has made it possible to find and use this tissue in more than 90% of cases. This remains the conduit of choice in revascularizating patients with gangrene. Thus, it has proved important to search for a suitable venous bypass in those patients (as many as 30%) from whom the long saphenous vein has been removed.

Experience teaches that using an autogenous vein for distal bypass, whether reversed or in situ, achieves long-term patency in 80% of limbs and that the percentage of amputations prevented exceeds 90%.

Even when prosthetic bypasses must be used, knitted Dacron and expanded polytetrafluoroethylene now achieve five-year patency rates of 30% to 50%. Limb salvage rates

in these cases range from 60% to 80%. These figures are acceptable if a diligent vein search proves futile.

Nearly half of patients needing distal arterial reconstruction have diabetes mellitus; some suffer from renal insufficiency. Therefore, magnetic resonance (MR) angiography has become important in the preoperative preparation of patients with limb-threatening ischemia. Interventions, whether operative or by radiologic techniques, are increasingly being based on MR angiography alone. Data currently suggest that MR imaging is an important adjunct whenever conventional angiography does not identify a suitable target vessel. Some have suggested that it has greater sensitivity than conventional angiography for detecting distal runoff arteries in limbs with severe ischemia.

Bypass techniques have also changed. Using a distal origin for the distal reconstruction has become routine. Results of such reconstructions with regard to patency and in preventing amputation are virtually identical to those of operations using the older, femoral artery inflow techniques. Bypassing to target vessels in the foot and ankle is also being done frequently. An added benefit of such reconstructions in patients with advanced ischemia is the prevention of amputation in 90% of patients.

Even persons 80 years and older benefit from limb revascularization despite their abbreviated life expectancy. Although the operative mortality nears 5% (compared with 1.5% for younger patients), the graft patency rates (66% at three years) and limb salvage rates (90% at three years) allow ambulation in 88% of patients, 85% of whom are living at home.

Lower extremity arterial reconstruction has progressed rapidly, distally, and successfully to the benefit of many patients with the severest forms of atherosclerosis.

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Alerts, Notices, and Case Reports

Pentoxifylline for Ischemic Pain in Pseudoxanthoma Elasticum

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PSEUDOXANTHOMA ELASTICUM is a multisystem connective tissue disorder characterized by degenerated and calcified elastin fibers.[1] Skeletal muscle pain due to ischemia is a common symptom, yet effective therapy for this has not been available. We report the case of a patient with pseudoxanthoma elasticum who presented with symptoms suggestive of abdominal wall and lower extremity ischemia. Treatment with pentoxifylline and a subsequent n-of-1 trial of pentoxifylline versus placebo caused a pronounced improvement in this patient's symptoms and exercise tolerance.

Report of a Case

The patient, a 43-year-old woman diagnosed with pseudoxanthoma elasticum by skin biopsy at age 27, presented with symptoms of crampy abdominal and bilateral lower extremity pain. This pain was exacerbated by activity and was described as "nagging, chronic, and burning." She had been noting the symptoms with increasing frequency and intensity for about four years. Her resultant inactivity had caused a recent 9-kg (20-lb) weight gain.

Additional significant medical history included chronic low back pain due to spondylolisthesis, migraine headaches, and a total abdominal hysterectomy and bilateral salpingo-oophorectomy for endometriosis. Her medications at presentation were propranolol hydrochloride (long acting), 80 mg once a day; ibuprofen, 400 mg three times a day; and estradiol, 1 mg once a day.

On physical examination she had the classic lentiform, patchy skin lesions of pseudoxanthoma elasticum at the web of her neck, angioid streaks on both retinas, and symmetrical tenderness to palpation of her lower abdomen and lower extremities. Her peripheral pulses and neurologic system were within normal limits, as were basic laboratory test results, including those of a complete blood count, chemistry panel (SMA-12), chest radiograph, and 12-lead electrocardiogram.

A recent gastrointestinal evaluation including abdominal ultrasonography and upper and lower tract endoscopy had found only mild gastritis. A regimen of pentoxifylline was started because of its ability to decrease tissue hypoxia caused by compromised microcirculation.[2,3] On an oral dose of 400 mg three times a day, the patient began noting lessening of her pain and improved exercise tolerance after two weeks. After four weeks on this regimen, she was walking regularly and had lost 5 kg (11 lb). The tenderness noted on previous physical examinations was gone. After several weeks, during which time the patient's symptoms had essentially resolved, the pentoxifylline was discontinued.

Methods

An n-of-1 double-blind, placebo-controlled crossover trial was initiated to assess if the patient's improvement could be ascribed to a placebo effect.[4] Three pairs of trials were planned using the model described by Guyatt and co-workers, with a ten-day washout period between interventions. The end point designating a failure of therapy was findings of any one of three signs or symptoms on bimonthly clinic visits: tenderness to palpation in the lower abdomen and extremities, pain with walking, and exercise tolerance of less than a block on level ground. Benefit of therapy was designated as the absence of these findings after two weeks' intervention. An investigational pharmacist prepared identical placebo and pentoxifylline capsules that the investigators and patient could not differentiate.

Results

The patient began taking capsule A after a washout period and the return of her symptoms. After two weeks she returned to the clinic saying she had no pain with ambulation, which allowed her to walk as much as two miles a day. No notable tenderness was found on physical examination. Capsule B was then substituted for A. The patient called after a week, saying the tenderness had returned and she could not walk a block without pain. A physical examination confirmed these findings, and the patient requested that we break the code. She had correctly identified the agent and placebo after each change. The patient, unwilling to spend further time without pentoxifylline, would not agree to further trials. Because of her dramatic response to the drug before and during the trial, we felt a clinically relevant answer had been obtained.

Discussion

Pseudoxanthoma elasticum is a multisystem disease involving predominantly the skin, eyes, and cardiovascular system. It is genetically heterogeneous, with prevalence estimates ranging from 1 per 40,000 to 1 per 160,000 live births.[1,5] Associated complications include gastrointestinal bleeding, presenile dementia, peripheral neuropathy, epilepsy, hypothyroidism, massive uterine bleeding, and first-trimester miscarriage.[1]

The cardiovascular complications are characterized by hypertension and premature atherosclerosis with predom-

(Takaro TK, Coodley GO: Pentoxifylline for ischemic pain in pseudoxanthoma elasticum. West J Med 1993; 159:689-690)

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inantly peripheral arterial occlusive disease.[5,6] These lesions are thought to be due to elastin degeneration in the arterial tunica media with secondary deposition of calcium.[6] Angina and claudication are commonly seen.[1,5,6] There is no standard effective therapy for the disorder or for its ischemic symptoms.[6]

Pentoxifylline is an orally active hemorheologic agent. It is a xanthine derivative that inhibits adenosine 3′,5′-monophosphate diesterase and increases intracellular cyclic adenosine monophosphate secretion.[2,3] It is used to treat conditions characterized by compromised regional microcirculation, most commonly peripheral vascular and cerebrovascular disease.[2] Pentoxifylline reduces hypoxia in the microcirculatory vascular beds by improving blood flow, primarily through changes in the vascular wall and increased fluidity of the blood.[3,7,8] In addition to improving microvascular blood flow, pentoxifylline may also act by reducing inflammation in the vascular bed because it inhibits the release of tumor necrosis factor and interleukin-1.[7-9]

N-of-1 trials are designed to assist clinicians in management decisions. The technique is used to justify individual therapy when large, randomized control trials have not been done or where individual response to therapy or dose is highly variable. Common areas of study are antidepressant use for chronic pain syndromes, response to therapy for reactive airway disease, and myasthenia gravis.[4]

Because we could not complete our original plan of three pairs of interventions, a problem often found with n-of-1 trials, we could not demonstrate statistical significance in this study. But the trial did clarify management in this patient, thereby fulfilling Guyatt and associates' clinical criteria for a "definite trial."[4] The drug was shown to be efficacious for this patient's pain, and this benefit was shown not to be a placebo effect.

After this trial, a second patient with pseudoxanthoma elasticum, a 43-year-old otherwise healthy woman, presented with right arm pain with exertion. She was started on a regimen of pentoxifylline, 400 mg orally three times a day, and returned two weeks later with complete relief of her arm pain.

Although there are no previous reports of pentoxifylline use in pseudoxanthoma elasticum, its benefit for these patients and in other dermatologic disorders characterized by microvascular ischemia is encouraging.[10] Larger trials are needed to confirm that pentoxifylline is useful in patients with pseudoxanthoma elasticum.

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Rothia dentocariosa Endocarditis

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Rothia WAS FIRST DESCRIBED as a genus in 1967 by Georg and Brown and shown in 1969 to be pathogenic but of low virulence.[1] This aerobic organism is gram-positive and varies in form from coccoid to filamentous to rod shaped. Branching is seen at times in the filamentous form, which thus resembles *Actinomyces, Corynebacterium,* and *Nocardia* species.[2-4] It is a component of normal oral flora that can be recovered from dental caries and plaque.[3,5] Since its original description, well-documented cases of infection establishing *Rothia dentocariosa* as a human pathogen have included periodontal inflammatory disease,[3,5] an infected pilonidal cyst,[6] a periappendiceal abscess,[7] five cases of endocarditis,[1,8-11] and an infected arteriovenous fistula.[2] The organism has also been identified by the Centers for Disease Control and Prevention in 39 specimens, but the clinical role of *R dentocariosa* in these cases was not defined, and the organism's infectious role was speculative. In this report I describe a case of *R dentocariosa* endocarditis involving a prosthetic valve that was successfully treated with antibiotics alone.

Report of a Case

The patient, a 71-year-old man, underwent aortocoronary bypass grafting with a Starr-Edwards aortic valve replacement in 1977. Fourteen years later, a week before he was admitted to the hospital, he noted malaise, bilateral lower extremity myalgias, chills, and a transient temperature elevation to 39.4°C (103°F). Initially treated symptomatically as an outpatient, he was admitted on November 22 with the diagnosis of prosthetic valve endocarditis when cultures of two blood specimens obtained at the office visit grew a gram-positive bacillus. He had no arthralgias, skin rash, diplopia or other neurologic symptoms, or recent invasive procedures. On physical examination at the time of his admission, the patient was afebrile, no Roth spots were noted, and the integument was normal.

(Ruben SJ: *Rothia dentocariosa* endocarditis. West J Med 1993; 159:690-691)

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Results of both the neck vein and chest examination were normal. Examination of the heart revealed a quiet precordium. The prosthetic valve sounds were crisp. No gallops or murmurs of valvular insufficiency were found. The abdominal examination revealed no abnormalities.

On admission to the hospital, four additional blood specimens were obtained for culture, and a regimen of vancomycin hydrochloride, 500 mg intravenously (IV) every six hours, and gentamicin sulfate, 60 mg IV every eight hours, was started. After preliminary sensitivities became available on November 27, the patient's regimen was changed to penicillin, 2 million units IV every four hours, plus gentamicin, 80 mg IV every 12 hours. In anticipation of home IV antibiotic therapy, the regimen was then switched on December 3 to ceftriaxone sodium, 2 grams IV every 24 hours. After four days of receiving this antibiotic, the patient became febrile again, and his therapy was changed back to penicillin, 3 million units IV every six hours, which was continued for the duration of the patient's 42 days in the hospital. There was no change in his physical state or complete blood count during this febrile episode.

The admission chest x-ray film was stable, and serial electrocardiograms showed transient atrial fibrillation. A transthoracic and transesophageal echocardiogram revealed no vegetations, perivalvular leaks, or aortic regurgitation. The prosthetic aortic valve showed normal motion and no evidence of a periaortic abscess. Computed tomographic scans of the brain and sinuses revealed changes consistent with a recent infarct in the right temporal parietal region, but no evidence of paranasal sinus infection. The Westergren sedimentation rate on November 22 was 39 mm per hour and by December 22 had returned to normal at 12 mm per hour. A rheumatoid factor titer was positive at 1:80. An admission urinalysis revealed trace protein and 2+ reaction for occult blood with 80 to 100 erythrocytes per high-power field, both of which subsequently cleared. The leukocyte count was 7.4 $\times 10^9$ per liter (7,400 cells per μl) with a normal differential cell count; a hematocrit was normal at 0.41 (41%).

Four blood cultures grew a gram-positive branching bacillus; cultures of 12 additional specimens taken throughout the hospital stay were sterile, including three that were taken when the patient became febrile while on ceftriaxone therapy. Sensitivities indicated that the organism was sensitive to ceftizoxime, ceftriaxone, cephalothin, chloramphenicol, imipenem, penicillin, and vancomycin, with intermediate sensitivity to erythromycin, gentamicin, rifampin, and tetracycline. The organism was resistant to amikacin, ciprofloxacin, kanamycin, and the combination of trimethoprim and sulfamethoxazole. By December 5, the organism had been identified as *R dentocariosa*. Dental consultation revealed disease and decay at teeth 11, 18, and 19. While receiving intravenous penicillin, the patient had his teeth cleaned, and teeth 18 and 19 were extracted.

After discharge from the hospital, follow-up blood cultures were negative, and both the Westergren sedimentation rate and the leukocyte count remained normal.

Discussion

Previously reported preexisting valvular disease in cases of *R dentocariosa* endocarditis included two cases of mitral valve prolapse with myxomatous degeneration,[8,9] a bicuspid aortic valve,[1] and rheumatic mitral valvular disease,[10] none of which required surgical intervention; one patient with mitral valve prolapse required valve replacement.[11] Only two of the patients had recently undergone dental manipulation.[9,10]

Antimicrobial susceptibility is sketchy, but *Rothia* species have been determined to have in vitro susceptibility to the penicillins, erythromycin, vancomycin, cefazolin, rifampin, aminoglycosides, tetracycline, chloramphenicol, and trimethoprim/sulfamethoxazole; susceptibility to clindamycin has been variable.[2] Patients with endocarditis were treated with penicillin G with or without gentamicin or streptomycin. An apparent relapse has previously occurred with vancomycin therapy.[8] Although minimal inhibitory concentrations, minimal bactericidal concentrations, and serum concentrations of ceftriaxone were not measured in this patient, I question the adequacy of ceftriaxone as single-agent therapy for *R dentocariosa*, even though a drug reaction or subtherapeutic dosing cannot be confidently excluded.

Summary

Despite its presence normally in the mouth, *R dentocariosa* appears rarely to cause infection outside the oral cavity. There is no doubt, however, as additional reports accumulate, that this organism should be recognized as having the ability to cause a serious illness in humans. In addition, in vivo experience seems to suggest that a penicillin regimen should remain first-line therapy for this infection, with the efficacy of other agents remaining unproved.

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Special Article

The Urban Poverty Crisis
An Action Agenda for Children and Youth

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In this unique society—probably the most technically advanced, affluent, and democratic the world has ever known—the crucially formative years of childhood and adolescence have become battlefields, literally as well as figuratively. Our schools as well as our hospitals and our streets are littered with avoidable casualties. The time has come to make a nationwide, research-based effort to reduce greatly the killing, maiming, and enormous waste of talent.*

During the past decade, the Carnegie Corporation has been supporting research and innovative practices to find paths out of severe poverty—partly by strengthening the current generation of adults to the maximal possible extent and partly by helping children and youth to fulfill the American dream by moving upward. These promising lines of inquiry and innovation provide the factual basis for this essay.

Despite powerful constraints, creative efforts in a variety of American cities have achieved remarkable results. Such interventions usually provide part of what a vigorous, cohesive, intact family would optimally provide—in an era of drastic family transformation related to massively changing technologic, economic, and social conditions. Such interventions give steady encouragement, stimulation, and guidance to children to pursue education and protect their health.[1]

To meet the requirements for healthy child and adolescent development, intervention should start early with family-equivalent functions. The pivotal institutions are schools, churches, community organizations, and the health care system—all augmented by educational functions of the media. A developmental sequence of interventions starts with prenatal care and goes on to preventive pediatric care, parent education, social supports for young families, high-quality child care, and preschool education. The next step is upgrading of the elementary and middle grade school experience because these schools develop partnerships with strong sectors of American society.

Many of the causes of damage to children are interrelated and potentially preventable at reasonable cost. A vivid example is prenatal care—now weak or absent for at least a quarter of pregnant women in the United States. Yet prenatal care has a powerful capacity to prevent lifelong damage and is highly cost effective. To fulfill this potential, collaborative work across disciplines will be necessary—both within and beyond medicine. At its best, prenatal care is a two-generation intervention that helps both children and parents.

Prenatal Care

High-quality, early prenatal care for all pregnant women is the essential building block for children's healthy development. It should include vigorous outreach efforts to bring poor young women into prenatal care early. Models exist that show this can be done even in very low income communities.[2]

The essential components of prenatal care are medical care, education, and social support services. The medical care functions are effectively synthesized in a recent report from the United States Public Health Service.[3] The other functions are less well known. Education begins with prenatal care because early, effective care protects the vulnerable brain of the growing fetus, thus allowing the child later to develop its full learning capacities; and it makes use of the distinctive motivation of the pregnant mother as well as the young father to strengthen their knowledge and skill in caring for themselves and their prospective baby. Moreover, the educational component of prenatal care can be expanded to include a constructive examination of options for the life course—links to job training, formal schooling, or other education likely to improve prospects for the future of the young family.

In poor communities, young parents need a dependable person who can provide social support for health and education through the months of pregnancy and beyond. In a valuable set of innovations, pregnant adolescents are connected with "resource mothers." These are women living in the same neighborhood as the young mother. They have successfully raised their own children and learned adaptive skills most relevant to this sort of situation. They convey what they have learned about the problems facing young mothers and provide sympathetic, sustained attention and gateways to community resources. As a practical matter, this intervention that provides family-equivalent

*See also the editorial by L. H. Clever, MD, "Diseases Desperate Grown," on page 700.

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From the Carnegie Corporation of New York, New York.

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functions in poverty areas illustrates ways to organize social support for health and education in various community settings throughout childhood and adolescence.[4]

If the United States implements this enlarged vision of prenatal care, every year many thousands of babies could be saved. But save them for what? Further opportunities are needed to foster healthy child and adolescent development. Evidence is accumulating that interventions in the first few years and then in early adolescence can shape a person's lifelong course in healthy, learning, constructive ways[5]:

- Well-baby care with emphasis on disease prevention and health promotion;
- Parent education to strengthen competence and build close parent-child relationships;
- Social support networks in which parents give mutual aid to foster health and education for their children and themselves;
- Child care of high quality outside the home, especially in day care centers;
- Preschool education in the Head Start mode; enhanced education in elementary and middle grade schools; and
- Constructive activities beyond school hours in community-based organizations.

Such interventions have strong potential to prevent damage as reflected in indices of health and education.

Preventive Health Care

Well-baby care oriented to preventing lifelong damage is vital not only for child health but for building parental competence.[6] Immediately after delivery, the pediatrician or other primary caregiver assesses a newborn's health and informs the parents. Attachment between mother and baby is fostered, and preparation for coping with predictably difficult episodes is undertaken. In addition to providing immunizations during infancy, such care also monitors a child's growth carefully to detect nutritional problems and provides early treatment of infectious diseases. This care gives well-informed guidance and emotional support to help families attain healthy lifestyles. Caregivers answer parents' questions and anticipate questions about growth and development, stress, and coping. They provide vital services—for example, early treatment of ear infections and correction of vision deficits so that hearing and visual impairments do not interfere with education.

Because pediatricians and other physicians are often in short supply, particularly in poor city neighborhoods and remote rural areas, it is essential to extend their reach. We need to enlist the aid of pediatric nurse practitioners, home visitors, parent support group workers, and public health workers. They can have an important role in building parental competence—through guidance about meeting requirements for healthy child development and as a gateway to community resources.[7]

In 1989 a distinguished national group of health leaders surveyed the prospects for child health in New York City, a prototype of urban health problems across the nation.[8] This commission described the nature and scope of the health problems and the steps we need to take in the 1990s to give every newborn the opportunity for a healthy start. Models exist for high-quality health services that could greatly diminish the current burden of illness and disability. Five crucial aspects of high-quality child health care were specified.

Aspects Required for Child Health Care

Comprehensive. Services should include not only sound medical care but also health education and psychosocial services to help prevent disease in early life. Convenient access should be available through primary care to community resources.

Continuous. Each child should have a durable relationship with one health care professional. That person should get to know the child and the family.

Coordinated. Health care should be connected with school, preschool, social services, and specialized care as needed.

Accessible. Outreach is essential. Services must have hours and locations that accommodate hard-to-reach families; they must be prepared to deal with language and cultural barriers.

Accountable. Every program needs systematic quality control so it can meet high standards of pediatric care, including prevention.

These desiderata for poor communities constitute something more than a hypothetical ideal. A concrete example has been of national importance over several decades: community health centers, originally known as neighborhood health centers. They still flourish in various parts of the country despite inadequate funding. They offer a range of medical and support services in the community and have proved their accessibility to low-income populations. Some of these centers have been carefully evaluated, and the evidence of their value is clear. Similarly, New York City has had for some years Maternity Infant Care Projects, which offer free and comprehensive services to pregnant women and their young children. Studies have shown that these projects provide prenatal care effectively and reduce the number of low-birth-weight babies among high-risk women. They also bridge the transition from maternity care to infant care.

Immunization

The most effective preventive medicine for infants is immunization against the common infections of childhood.[9] Clearly the best course to pursue is comprehensive immunization at appropriate times in the earliest years.

Most American school-aged children are fully immunized, largely because of mandatory immunization for school entry. Yet less than half of poor and minority children younger than 4 years are fully vaccinated against the preventable infections of childhood. Tying immunization to day care and preschool education can be helpful in ways analogous to requiring immunization for school entry. A system of comprehensive primary care would be best for this and other purposes.

Immunization has provided a valuable model—and indeed an inspiration—for preventive interventions of various kinds. Although other preventive interventions differ in important ways, some basic concepts are transferable: understanding the nature of the damaging agent and how it works to produce harm, understanding the human responses that can naturally confer protection, finding ways through research to simulate the body's own protective responses, educating the public to make effective use of the intervention once available, and, finally, public sector support for the widespread application of effective interventions.

Adaptability of Health Care

An important component in dealing with the problems of poor communities is to increase the adaptability of the health care system, not only because it is so important in its own right in relation to the serious health problems of the inner city, but also because it presents great opportunities as a point of entry for help of various kinds—using not only health care referrals but also the educational system and social service agencies. The health care system taps into crucial survival motivation that is certainly not lacking in poor communities. In this context, several points of intervention are particularly important: prenatal care, with its outreach to provide early care in the first trimester and to build in an educational and counseling component; the emergency department, which is the first point of contact for many poor people and the source of much primary health care; and school-related health facilities such as clinics based in or near schools. In the computer era, it should be possible to have in every community an accessible source of information about all community resources applicable to healthy child development.

Parent Education and Family Support

A substantial amount of research in child development makes clear that intervention programs can help parents become teachers of their own children—at least to make clear to their children the strong value they put on intellectual achievement and constructive human relations.[10] It has increasingly been shown that these are matters not only of cognitive stimulation but also of emotional and social development. So intervention programs now provide emotional encouragement, cognitive stimulation, and social support. Research has shown that quality day care plus parent education can yield strong results in cognitive and social development during infancy and early childhood in high-risk urban poverty populations.[11] Often the adolescent mothers involved in these intervention efforts benefit as manifested by their going on to higher levels of education; and there is some evidence of beneficial effects on younger siblings. Like prenatal care, this can be a two-generation intervention—benefiting young parents and their children, even for the entire life span.

Preschool Education

The main experience with preschool education is at age 4, though there is considerable work at age 3 as well. Head Start and similar programs have become symbols of hope over three decades.[12] Overall, children who have been in early education programs like Head Start have shown better achievement scores in elementary school, are less likely to be classified as needing special education, have higher rates of high school completion and college attendance, and lower pregnancy and crime rates than comparable students who were not in preschool programs.[13]

The lessons of Head Start have wide applicability. This kind of early stimulation, encouragement, instruction, and health care—all with substantial parental involvement—can also be incorporated into a variety of child care settings, and thereby help to reduce casualties. The linkage of health and education is fundamental in these interventions. This approach is spreading to age 3, and the basic concepts can be usefully adapted to earlier ages. But Head Start is *not* best seen as a one-time event—akin to immunization. Rather, it is a valuable part of a development-promotion sequence throughout childhood and adolescence.

Home Visiting

Home visiting by human services professionals can be a relatively efficient and effective way of addressing the many needs of poor families with young children.[14] Home visitors can engage family members in solving problems of housing, food, health, child rearing, child development, and family relationships.

Workers can use home visits to instruct and motivate mothers, listen to them, observe them interacting with their children and other family members, and discuss service needs. A particular program typically uses home visits to tackle more than one problem.

Home visits can be an effective way to teach parenting skills to high-risk families who suffer from multiple stresses and even clinical depression. Such families are the least likely to come to health clinics for prenatal care or well-baby checkups, to participate in parent education classes, to attend parent support groups, or to seek quality preschool programs for their children. They are at relatively higher risk than other parents for abusing or neglecting their children.

Research evaluations of home visiting programs show that they can have beneficial effects on health and well-being, especially for poor adolescent mothers and their families. Families that have had the benefit of home visiting have lower rates of small-for-gestational-age and low-birth-weight babies, the babies are healthier at birth, have fewer accidents in the first year of life, are immunized more often, experience less child abuse and neglect, and show improved cognitive performance. These benefits can be long lasting, as demonstrated by the best-studied early intervention programs aimed at preventing damage to disadvantaged children.

Healthy Adolescent Development

As children experience puberty and emerge into an era in which they feel they should quickly become adults,

they in effect ask, "How shall I use my body?" Any responsible education system must answer that basic question with a substantial life sciences curriculum that gives them accurate information about their bodies, including the effects of various high-risk behavior patterns.[15] But information is not enough.

How should good use be made of accurate and personally meaningful information? Life skills training can become a vital part of education in schools and community organizations, so that adolescents can learn how to make informed, deliberate, and constructive decisions—rather than ignorant, impulsive, and destructive ones.[16] Such training can also enhance their interpersonal skills, their ways of relating decently to others, learning from their experiences, even unpleasant ones, such as how conflicts can be resolved without violence. Skills can be developed for establishing dependable friendships and participating in supportive problem-solving groups. But even this is not enough.

People need people, especially to weather the inevitable difficulties of growing up, the stresses of education, and the turbulent search for ways to protect our own health and the health of those we care about. To the extent that contemporary families are unable to meet these needs, specially designed social support interventions can be exceedingly helpful.[17]

Thus, the life sciences curriculum linked with life skills training and social support interventions can provide the vital information, skills, and motivation necessary to meet the requirements for healthy adolescent development.

Moreover, this conjunction of information, skills, and motivation for development, indeed for survival, can be provided through the foresight and cooperation of several pivotal institutions that powerfully shape the transition from childhood to adulthood: family, schools, health care system, media, and community organizations that reach out to youth.

But there is still a serious unmet need for accessible health care. It may be at or near the school. In any event, it must be arranged in such a way that middle grade students can clearly recognize that the care is available, within reach, and adapted to their distinctive needs.[18]

Substance Abuse Prevention

In the past few years, there has been a good deal of public talk about education as a means of preventing drug abuse. Although this discussion reflects serious concern, it has so far given little indication of what is meant by education in this context. Is it straightforward information about the harmful effects of various substances? If so, what reason is there to think that such information will be sufficient? If not, what else could be added to make it effective? In general, what can research tell us about how best to proceed on this vital matter? Can the demand be substantially lowered? Can social norms regarding drug use be changed? Evidence is emerging that this is possible, even in poor communities.[19]

For changes in behavior for health to occur, three factors are needed: information, skills, and motivation. Education can contribute to all of these. Through education in various channels, motivation may be strengthened and sustained, accurate information assimilated, and relevant skills developed. Such education involves not only the schools and health professionals but also the media. Family, churches, and community organizations can contribute as well. In poor communities, a key element in motivation is the perception of opportunity. Without such perception and concomitant hope, there is little incentive to avoid the immediate pleasures associated with psychoactive drugs.

Recent school-based and community-wide preventive interventions have been carried out in careful research designs. These focus on cigarette smoking but have made some extension to alcohol and other drugs as well—"gateway" substances. The results are clear: It is feasible to diminish substantially the use of gateway substances in early adolescence. Moreover, this can be done in a way that enhances personal and social competence pertinent to other aspects of adolescent development. In school and out, it is possible to build competence, to earn respect, to construct a friendship group capable of resisting pressure to use drugs, and to delineate a vision of an attractive future and prospects for a decent life.[20] An important part of this in poorer communities has to do with making early opportunities visible to young people before the drug pathway becomes firmly established. Work-study activities are helpful in this regard, along with training in essential, generic employability skills and accurate employment counseling.[21]

Drug taking may be considered to some extent as self-medication for distress, a kind of stress management or high-risk coping behavior. More generally, drug taking may be seen as coping behavior oriented toward the transition to adulthood—a way of feeling big, strong, courageous, or otherwise grown up. There are ways to move in this direction that are more effective and less dangerous. The learning of coping skills has been applied increasingly during the past decade, especially in studies of adolescent preventive interventions with respect to smoking, alcohol, and marijuana. Such interventions provide positive, constructive alternatives to the heavy use of psychoactive substances. They provide pathways toward healthy adolescent development.

Overcoming Disadvantage

For the child growing up in an area of concentrated poverty, two crucial prerequisites to healthy, constructive development appear to be lacking: secure attachments to dependable and successful adults, and the perception that opportunities exist in the mainstream economy. To the extent that families and communities are eroded, disintegrated, or otherwise weakened under circumstances of persistent poverty and social depreciation, it is necessary to focus on other social support networks—by strengthening the family or by providing substitute experiences that meet these essential needs.

With younger children, social supports have to be-

come a deliberate feature of effective interventions throughout development: in prenatal care, child care, preschool education, after-school and Saturday experiences during elementary years, and in the reform of the middle grade schools. At every level, in some developmentally appropriate way, it is possible to construct parent groups, parent education, outreach to families through indigenous paraprofessionals, and links with professionals as needed for more serious problems. Education of disadvantaged minorities needs to incorporate social support networks that sustain effort and hope.

A variety of organizations and institutions can provide supplements or even surrogates for parents, older siblings, and an extended family. Across the country there are encouraging examples of such interventions.[22] Some are based in churches (such as the initiative of the Congress of National Black Churches), some are based in community organizations (Boys and Girls Clubs), others involve youth service (Campus Compact, based in colleges and universities), and others are based in minority organizations. The central point here is that churches, schools, community organizations, and businesses can build constructive social support networks that attract disadvantaged youngsters in ways that foster their health, their education, and their capacity to be accepted rather than rejected by the mainstream society.

Recent experience suggests the promise of mentors for poor children. Various minority organizations have been providing mentors from similar backgrounds for inner-city youth. For example, minority college students have in some cases devoted three evenings a week for tutoring, joint recreation, experience in gaining access to community resources, and developing social skills. These activities are generally attractive to adolescents, and may combine entertainment with education. A recurring emphasis in such efforts is on forming constructive human relationships, providing models of accomplishment and success, developing skills pertinent to the mainstream economy, building self-esteem, and seizing real opportunity.

Conclusion

Our prodigious capacities for technical innovation and social organization could be mobilized to diminish human impoverishment greatly in the decades immediately ahead. Research and experience in different parts of the world suggest several basic needs that must be addressed in efforts to emerge from poverty. All are technically feasible and well within human capabilities, yet fulfilling these needs is an exceedingly difficult task. What is required?

- *Adequate health.* A major pathway is through science-based disease prevention from the time of conception onward. A crucial element is the formation of healthy lifestyles in childhood and adolescence.
- *Education for crucial skills.* Whereas education must be valued for its own sake in every sphere of human inquiry, those skills must be emphasized that are most salient for survival and well-being in a particular setting and most likely to earn income and respect. This involves not only cognitive and technical skills but interpersonal and organizational skills as well.
- *Mutual support.* To achieve good health and develop crucial skills, humans need dependable social support networks—family, friends, community—groups that provide a sense of secure belonging. Such support networks tend to provide mutual aid in the face of the inevitable stresses of living, to facilitate healthy lifestyles and continuing education, and to provide opportunities.
- *A structure of opportunity.* Given the biologic variability among humans, vastly diverse aptitudes and talents are found among children. For these latent qualities to come to fulfillment, they need open paths. A child's chances can be enhanced by an intact family and other responsible, caring adults. But a larger structure of opportunity is also necessary—a mutually supportive network not only in the child's community of origin, but also in the larger society—and it must be protected by law in an open economy.

We can make many constructive responses to the casualties of early life. Some interventions are well documented. Others are promising, but the research is too limited for definitive answers. We can make substantial progress by deepening our understanding of human development, by fostering public understanding of our children's urgent needs and opportunities, and by strengthening our scientific and professional commitment to tackle these problems over a wide spectrum of constructive approaches.

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* * *

LIMB

for Nelson Mandela

Let him who in a fixed moment was exiled in his own
Homeland and robbed of a future

Flush with the common sights and small
Pleasures the poor are permitted, let him

Go now with open eyes down the sunset way
No longer having to take it all in alone, crowned

King simply by stepping out for a walk
In the one world quarantined beyond

The cyclone fence where, after rain, there's a sweet
Tang in the air of metallic

Freedom. Let those denied
That half of the world women bring with them

For a while into this one, who see
Things others have learned

Not to see in the unavoidable gunfire,
And not been broken

In the seeing, let them be the break in the chain
Of command from Sarajevo to Soweto.

Those who have been there often gleam
In times of crisis with knowledge

Of what can happen to you there. Long after,
it's never over, never

missing, like a lost limb's aching,
anchoring pulse, a living thing once within limits,

agonizing towards completion.

JACK MARSHALL©
San Francisco, California

Commentary

Labors of Love and Care

RANDALL WEINGARTEN, MD, *Stanford, California*

A group of medical colleagues has been meeting weekly for more than a decade. In time our clinical discussions have become a labor of love reflecting the slow, mysterious growth of devotion among us: to the well-being of our patients, to each other, and to our profession. This has not always been a smooth curve.

At a recent breakfast discussion, two members of the group—one in his late 50s, another in his 40s—described their preparations for the national board examinations in their specialty. They had been studying incessantly. Each had attended an expensive, week-long review course. They had taken multiple practice examinations and had sharpened their minds for making fine distinctions.

Our talk happened to coincide with the airing earlier in the week of Bill Moyers's three-part public television special "Healing and the Mind." In his good-natured, candid, slightly skeptical style of journalism, Moyers plunged into the misted realm of the mind's role in healing and in encouraging health. He turned first to world cultures that have ancient traditions of healing using spiritual and mental practices. Sometimes through interpreters, some of whom were western physicians, and sometimes directly, he engaged several Asian masters of healing about their work. We watched him questioning, participating in, and musing about their teachings of meditative movement, their influencing the channeling of invisible life energy, *chi*, and their respectful combining of spiritual, physical, and social approaches in caring for chronic illnesses. We shared his gentle but firm probings of their structures of beliefs about illness and healing. We listened to how patients and students respond to their ministrations, their teachings. These are the wise ones.

Turning to our own culture of medicine, Moyers presented several inspiring examples of the permeation of these notions of the mind's role in healing into clinical action: a physician in Massachusetts teaching meditation practice to groups of persons suffering with intractable pain; a psychiatrist at Stanford investigating the effects of support-expressive group discussions on long-term survival for women with breast cancer; a private health-care group in California that uses a retreat format for enhancing living and well-being in the face of chronic or life-ending illnesses.

Throughout his inquiry into these old healing-helping cultures, Moyers was intent on exploring the mysterious role of the mind in healing. Who are these wise masters, what do they know, and what is the true nature of their skillful means? Every ancient culture of healing has its own angle on the mind-body problem.

In our discussions, we wondered about the effect our colleagues' studies were having on their clinical practice. One noticed that his personal growth in confidence, knowledge, and sense of competency was paralleled by his awareness that several of his patients did not appreciate, even resented, his absorption. Most patients had noticed the signs of intense preparation in his office. Some directly expressed their feelings of rejection, of hurt at his apparent distance.

They felt he was not there for them in the same way. In fact, he acknowledged, he had been preoccupied. He was finding studying for the specialty board examinations exciting and absorbing. He relished the sense of being up on the latest information, of unifying his knowledge. His sense of the magnitude of changes in scientific knowledge since his earlier training was humbling. By grasping this new knowledge, he felt he was increasing his ability to be helpful as a physician. Yet the more he jammed his mind with facts from the late stages of 20th century medicine, the more he had to contend also with his declining memory. He felt anxious about passing the examinations, about his ability to compete with younger physicians just out of residency training.

Later that early spring day, while taking a walk between patient hours, I realized that these two events—the conversation about specialty board examination and reflections about the Moyers special—were quintessential aspects of an age-old tension between knowledge and wisdom. Here were two colleagues, each evolving into their own wisdom about clinical practicing and deeply absorbed with reviewing the modern scientific knowledge of illness, pathophysiology, and treatment in their specialty. Mirroring them was the Moyers program's depiction of masters of wisdom traditions who evolve and transmit knowledge in ways that mountains and rivers naturally share their understandings. The ground-plan of their health science, knowledge, and wisdom tradition diverges from our own in the West. Yet it, too, is vital and helpful. How is it possible we can exist in such different

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domains, can evolve such alternative practices and beliefs, yet realize such vital results—each in our own way?

It may be said that knowledge abounds, but wisdom gleams. And between the two is something rarely studied or taught, except through embodiment: wise clinical judgment. In western medicine, a science of medical decision making and medical informatics is evolving rapidly. It soon will become a full discipline within the zone between clinical medicine and computer science. We must all welcome this new possibility, yet reserve our opinion of its place in the ancient tradition of wise clinical judgment.

I recall now the lines from W. B. Yeats's masterpiece "Leda and the Swan." As Zeus, in the guise of a great swan, rapes Leda, the wise poet asks,

> *Did she put on his knowledge with his power*
> *Before the indifferent beak could let her drop?*[1]

He does not ask about her gaining of wisdom, nor the meaning of wisdom in relation to knowledge. Yet it is just this wisdom, the infinitely subtle blending and unification of love, compassion, devoted awareness, knowledge, and a sense of justice with mercy that is so at the heart of humanistic medicine, eastern or western.

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* * *

CONSTELLATION CAT

(A Migraine Aura)

The constellation cat
slinks along the visionfield
unbidden. Settles in, stretches out;
an omen.

The feline blackness deepens
as the starry outline brightens.
The comet-tail swishes,
white lights dancing.

Crouching now, energized,
he leaps high, falls
in a brilliant ball
spinning.

Mid the whirling orb
a black hole waxes;
swallows the lights,
puts out the cat.

MARCIA DENIUS©
Indian Harbor Beach, Florida

WHERE GALLINULES MEW

It seemed robust, that pine,
its needles silver in the sun
as if still wet with dew. You never knew
it hid on its eastern face a blotch
of browning cones. Your disease was quick,
your healthy mind no curb to cells
that raced like a street gang,
wild to execute a contract.
You were gone a year when two trucks
rumbled over the fairway with men
and chain saws. From your chair
on the deck I watched the young men
climb the tree, felt the quiver
of its brittle limbs at the bite
of the blade.

Now, as I round the pond by the cattails
where gallinules mew like kittens and bull-
frogs play ventriloquist, I am stunned
by the sight of the stump they left.
Still as a willow when the wind dies
I remember how it was with you and me.

HELEN M. COPELAND©
Charlotte, North Carolina

Editorials

Diseases Desperate Grown

Diseases desperate grown by desperate appliance are relieved, or not at all.

WILLIAM SHAKESPEARE
Hamlet. IV:iii, 9

WE HAVE A desperate disease in America: neglect of our children. We know that

- One of five children in the United States lives in poverty[1];
- 3.5 million children go to bed hungry[1];
- About 3,000 adolescents become regular smokers every day[1];
- 14% of boys and 13% of girls have been robbed at school[1];
- 3 million adolescents contract sexually transmitted disease every year.[1]
- From November 1990 to November 1991, the number of teens diagnosed with the acquired immunodeficiency syndrome increased 25%.[2]
- The most recent comparison of our infant mortality rate with the rest of the world's ranked the United States as 23rd, a drop from 20th in 1980.[3]
- Although total infant mortality in the United States dropped in 1990, the gap between African-American and white infants increased.[3]

Marian Wright Edelman, founder and president of the Children's Defense Fund, projected last year that, in America by 1996, if no immediate action is taken,

- 1,080,000 babies will be born at low birth weight;
- 143,619 babies will die before their first birthday;
- 15,856 children aged 19 or younger will die by firearms;
- 3,600,000 infants will be born into poverty.[4]

The children are not at fault. No one can blame a baby for having a low birth weight. In fact, blame is not the issue at all. The issue is, where do we go from here?

At bedrock, we need to believe that a society's worth is measured by the way it treats its most vulnerable members. Children are vulnerable. To advance vigorously, we need to agree that children are not only at risk but are also important. They are not necessarily more important than any other group, but they are important. They require attention and care. They are the future. There is a certain practical 1990s application of William Wordsworth's "The child is the father of the man." And that is, according to James Garbarino, PhD, a specialist in preventing and treating child abuse, "If we don't deal with the adolescents as victims, we will ultimately have to deal with large numbers of them as perpetrators."[5(p3)]

We need to understand the forces behind the data. Biology, psychology, and social factors such as family structure are important. Sometimes, frankly, because of inadequacy, selfishness, or worse, parents and others let children down, abandon them, do not meet their needs, reject them, ignore them, and otherwise hurt them. Children may be bereft of a strong sense of self, healthy body, an uplifting spirit. Poverty, poverty, poverty is not the only determinant, but it is a multiplier in many health problems of children. Children from low-income families have double the incidence of low birth weight, bacterial meningitis, and severe iron deficiency and triple the frequency of delayed immunization and lead poisoning.[7] Poverty, lack of education, and inadequate health care, housing, and nutrition are linked.

Although we need more information and analysis, we should push ahead now, doing the best we can. The stakes are high. Children are starting to smoke, drink, and use other drugs, on average, when they are 12 years old; the number of adolescents between 10 and 14 years of age will increase by more than 16% during the 1990s.[8]

We have learned that laws do not always deter. They do not stop young people from obtaining our number one killer, tobacco. A recent study of teenagers' access to tobacco products in Texas showed that signs required by state law were rarely posted and their presence did not prevent purchases anyway: most teens were still able to buy cigarettes.[8] If laws are not the whole answer, the mere presence of information and services is not, either. Rather, as David Hamburg, MD, president of the Carnegie Corporation, points out in this issue,[9] we need early, full, coordinated efforts by virtually all our institutions. We need to give attention to each child, not only "children" as an impersonal classification.

Can we do it? Can we relieve our desperate disease of neglected children? Can we put our shared values into action? Can we harness our spirit? Edith Wharton said, "There are two ways to spread the light: to be the candle or the mirror that reflects it."[10] Hamburg has illumined a reasonable, achievable way to save our children. Let's glow.

LINDA HAWES CLEVER, MD

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Predicting Outcome From Mechanical Ventilation

MANY ASPECTS OF traditional medical practice are undergoing fundamental change. Physical diagnosis, histori-

cally an intimate act performed with a minimum of technology, is increasingly based on elaborate laboratory testing, invasive diagnostic procedures, and computerized images. Prognosis, always an important but traditionally an informal aspect of a physician's consultation, is also being transformed into a more objective process using large databases and advanced statistical techniques.[1] The predictions resulting from such analyses, however, are neither as widely available nor as universally accepted as computed tomographic scans.

Like physical diagnosis, however, medical decision making is a combination of deduction—reasoning based on past experience—and intuition or professional judgment. When all of the diagnostic and therapeutic capabilities that physicians controlled were contained within a small leather bag, the consequences of physicians' decision making and their estimates regarding prognosis had little influence on the course of patients' illnesses and were of only minimal interest to society. Today's physicians are able to provide a wide range of useful and desired treatments that are likely to directly influence patients' outcomes. Choosing the most appropriate treatment from the wide variety available is increasingly difficult, but the consequences of such choices are growing.[2] Medical services now account for a seventh of this nation's economy, and decisions regarding appropriate use are of substantial interest to payers, politicians, and the general public.

How should physicians respond to these fundamental changes? Should they continue to rely solely on informal individual skills of prognostication for the deductive part of their medical decisions? Or should physicians investigate the value of more formal and objective techniques for estimating who may benefit from advanced medical care?

In this issue of the journal, Papadakis and colleagues report the findings of a Department of Veterans Affairs (VA) cooperative study on mechanical ventilation that provides important background to this discussion.[3] The study is a straightforward report of prognostic factors following mechanical ventilation for 612 medical patients admitted to the intensive care units (ICUs) of six VA medical centers. The results from this survey can be viewed from a number of different perspectives, but in this editorial, I will comment on what they mean in terms of the need for improved prognostic capabilities of physicians and health care systems.

The overall outcome results are striking: more than two thirds of the 612 patients died in the hospital, and by one year the death rate reached 77%. This means that for most patients admitted to ICUs, mechanical ventilation and associated intensive care were ineffective. At least three important consequences derive from this pattern of patient and treatment selection.

First, it means that many of these patients died attached to a ventilator. Having witnessed hundreds of such deaths in my 15 years as codirector of a medical-surgical ICU, I can attest that this is, at best, an impersonal way to end one's life. Normal communication is impossible, and the ventilator intrudes on family relations and personal dignity. I, and most of the American public, do not wish to die attached to a ventilator.

Second, it is detrimental to treating clinicians. Inserting tubes and placing a patient on a ventilator, and then restraining and sedating them so they "stay on the machine," are among the most aggressive forms of treatment provided by medical professionals. When it fails to achieve success in two thirds of the attempts, an ICU staff's morale decreases and their cynicism increases. This then adversely affects the care of other patients.

Third, it uses expensive and limited human and material resources. With all of the current attention in Washington focusing on the reform of our health care system, much is being said of administrative waste and efficiency. Knowledgeable observers such as Aaron and Schwartz emphasize, however, that any such potential savings are small and temporary compared to the larger ongoing costs associated with new technology-dependent treatments of illness.[4] The pattern of care described by Papadakis and associates is a good example of the challenge described by Aaron and Schwartz. It is also an example of expensive treatment provided to a few patients near the end of their lives. This is an important contributor to overall medical care costs and a complicated issue for physicians and policymakers.[5]

Some of the ways we might begin to look for assistance are suggested in this VA study. The authors report that short- and long-term death rates for subgroups of the population, defined by either age, severity of illness, or the initiation of mechanical ventilation following cardiac arrest, were as high as 91% and 98%. Could such estimates improve the precision of such difficult decisions as initiating mechanical ventilation? Two studies have suggested that such objective estimates may be useful in reducing the level of care for patients unable to benefit without decreasing the intensity of care provided to patients with better prognoses.[6,7] A recent study that focused on patients with head trauma found a substantial reduction in the number of patients with poor prognoses who were intubated and mechanically ventilated. More such evaluations need to be done.

In endorsing and conducting these studies, we must always recognize that these "high-cost/high-mortality" patients are among the most vulnerable members of our society. Medical determinations of priorities for care should be based on the best comprehensive analysis of medical evidence, not simple and incomplete summaries. Cohen and associates recently suggested using a combination of age and the duration of medical therapy to estimate likely benefit.[8] Although such estimates may assist in reducing the duration of mechanical ventilation, they would do little to decrease the proportion of patients dying on a ventilator. It is also inappropriate to use age as the only patient characteristic in a criterion for withholding or withdrawing ventilatory support. Our experience and research have convinced me that age is an important but relatively minor contributor to predicting outcome. Severity of illness is a far more important factor.[1] Basing

any decision to offer therapy on a single patient characteristic is neither necessary nor appropriate.

Estimates of prognosis can now be supported by large and current databases involving thousands of patients and containing a combination of medical facts on each person. Taken together, these facts—severity of illness, physiologic reserve, response to therapy—summarize a patient's ability to benefit from further treatment. Analyses of these facts can be displayed in numerical form, such as probability estimates with appropriate confidence intervals. These numerical estimates can then be combined with an assessment of other patient characteristics, particularly personal preferences and individual values, in a comprehensive attempt to arrive at the best possible treatment decision for a particular patient.

Papadakis and colleagues caution that their study does not provide this type of comprehensive analysis, nor do they endorse their results as providing guidance about who can and cannot benefit from mechanical ventilation. This caution is appropriate. Large contemporary clinically accurate databases are still not widely available. The database used in this analysis, while specific to VA patients, is now old, having been collected in 1986 and 1987. Because they have never been a part of medical reasoning, objective individual probability estimates currently lack precise meaning for most clinicians. Much work needs to be done in both developing estimates and learning how to best integrate them into clinical decisions. The introduction of such explicit numerical probabilities into medical decision making will inevitably change the nature of prognosis. They will not, however, provide definitive guidance. At best, they will increase the recognition that there are always alternatives and will prompt discussions of the value expected from treatment. It is hoped that they will also increase our knowledge and promote better communication among physicians, patients, and their families. Of course, numbers are not sufficient to address the complex challenge presented by the results of the study by Papadakis and colleagues. The wisdom and intuition that a good clinician needs to make better decisions contain many components. Prognostic capacity is only one aspect of this complicated process, but it is a place to start looking for improvement.

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Role of Platelet Adhesion and Aggregation in Antithrombotic Therapy

George M. Rodgers, MD, in this issue of the journal reviews antithrombotic therapy, old and new.[1] It is a field in rapid expansion, after years of relative stagnation dominated by heparin, warfarin, aspirin, and not much else. It is not unusual, when introducing the topic of future anticoagulants, to refer to ticks, leeches, snakes, and vampire bats (the sources of some of the drugs currently in clinical trial), perhaps as a way to signify that new directions are being pursued with unlimited imagination. Yet, the new drugs for the beginning of the next millennium will likely be designed for the purpose and not be derived from natural products, as exotic as these may be. The reasons to support this concept have begun to emerge from studies on the mechanisms of normal hemostasis and pathologic thrombosis: these two processes may be sufficiently different to allow some degree of selective inhibitory intervention; and, certainly, natural antihemostatic substances did not develop in nature to prevent thrombosis but to block clotting. Thus, natural products are not likely to target specifically those functional aspects that distinguish the formation of an occluding thrombus in a diseased artery from the formation of a hemostatic plug in a normal small artery or capillary. Future drugs, with maximal antithrombotic efficacy and minimal hemorrhagic side effects, will be keyed to inhibiting these distinctive pathways. As a corollary of such developments, because hemostasis and thrombosis are complex events, it is easy to predict that there will be several new drugs, each effective in a selective manner. They will be used in varying combinations rather than alone, depending on the nature of the underlying disease process and the area of the vasculature at risk of occlusion. Prevention, rather than the treatment of ongoing or established thrombosis, will be the main goal; and specific drugs will be used to protect people from the risks of vascular occlusion, different from those used to dissolve clots and avoid reocclusion.

Is this picture likely to become reality in the not-too-distant future? Perhaps, as suggested by the intense interest demonstrated by several investigators in the field. The market for new antithrombotic agents is large, being estimated in excess of 5 million patients per year in the United States alone; this should ensure the continued support of research efforts from drug companies. The areas of application that generate the most interest, reflecting the incidence and potential severity of the various thromboembolic diseases, are the ones that may involve platelets and the arterial side of the circulation. In other words, new antithrombotic drugs are being sought for use in the prevention and treatment of coronary artery

disease, cerebrovascular disease, and peripheral arterial occlusive disease. This is not to say that deep vein thrombosis and pulmonary embolism, diseases that represent at least a third or more of the total number of thromboembolic disorders, are not a topic of discussion for new antithrombotic agents; in fact, they are likely to benefit sooner from substantial progress, represented by low-molecular-mass heparin and specific thrombin inhibitors. Nevertheless, antiplatelet drugs, which appear to be the most promising possibility for new approaches to the prevention of arterial occlusion, are likely to represent the topic of most aggressive research. Substances that block thrombin activity and, thus, platelet activation may be considered as a special subset of this category, even though their action is reflected on aspects of hemostasis or thrombosis other than platelets (that is, clotting). The targeted selection of effective inhibitors of platelet function requires an in-depth evaluation of the role of these cell fragments in hemostasis and thrombosis.

Progress in elucidating the mechanisms through which platelets perform their role in hemostasis continues at a rapid pace supported by the application of powerful new techniques. Particularly in the past ten years, detailed knowledge has been acquired on the membrane receptors and adhesive ligands involved in the fundamental aspects of platelet adhesion and aggregation. Moreover, it is now well appreciated that hemodynamic forces, the consequence of blood flow in the vascular system, play an important role in determining the mechanism of platelet responses to vascular injury. Platelets contribute to the maintenance of the normal circulation of blood through the preservation of vascular integrity and the control of hemorrhage after injury. They survey the inner lining of the vessel wall without adhering to it under normal circumstances, but respond rapidly to alterations of endothelial cells by attaching firmly to the site of lesion, where subendothelial structures may have been exposed. The first layer of platelets is in contact with the thrombogenic surface, whereas subsequent growth of the hemostatic plug depends essentially on platelet-to-platelet interactions; these two functional stages represent "adhesion" and "aggregation," respectively.

The first step in the response of platelets to vascular injury is their irreversible attachment to the altered surface. This stage is influenced by an essential aspect of the regulation of platelet function, namely the ability to recognize the site of lesion as different from the normal vessel wall. Two possible mechanisms can be considered relevant in this regard: one, that substances (agonists) generated as a consequence of the lesion act on platelets in the proximity of the lesion and "activate" them so that they can interact with adhesive molecules in blood or exposed at the site of injury; another, that circulating "resting" platelets react with adhesive substrates exposed only where the vessel wall is altered. In the first instance, the regulation of platelet function would rest mainly in their transition from "resting" (inactive) to "activated," and, in the second instance, in the limited exposure of efficient adhesive substrates to which "resting" platelets can attach. In fact, a combination of both events is likely to occur during the formation of platelet thrombi; however, the response of resting platelets to a local adhesive environment created by the lesion in the vessel wall probably represents the initial response onto which the subsequent formation of a hemostatic plug is built. Indeed, it is possible that adhesion always precedes, and is necessary for, platelet activation.

The process leading to a thrombus capable of arresting hemorrhage involves necessarily the interaction of platelets with one another. This occurs after platelets initially adhere onto a thrombogenic substrate at the site of injury; this can actually be visualized as adhesion occurring onto already adhering platelets, or the cohesion of platelets. Like adhesion, it is likely to involve both the recognition of activated adhering platelets as an appropriate adhesive substrate by resting circulating platelets and the action of local agonists that activate platelets. In this regard, it is relevant to consider that a substantial proportion of the current concepts on the mechanisms of platelet aggregation are based on experimental models that study platelets in suspension, in the absence of a reactive surface. Nevertheless, aggregation may never precede adhesion during hemostasis in vivo.

The complex series of events that determine the occurrence of a normal hemostatic response or the formation of a pathologic thrombus, including chemical reactions that involve cells, the vessel wall, and molecules in solution, is influenced by the flow of blood. In a vessel, the velocity of blood near the wall is lower than towards the center; this difference creates a shearing effect between adjacent layers of fluid moving at different speed. Thus, "shear" is the consequence of the relative parallel motion between adjacent fluid planes during flow; it is greatest near the vessel wall and decreases progressively towards the center of the vessel. The local shear rate is expressed in centimeters per second per centimeter, or the equivalent inverse seconds (s^{-1}). Fluid shear stress is the force-per-unit area that can be seen as the underlying cause of the shearing motion of blood. The shear rate is directly proportional to the shear stress and inversely proportional to the viscosity of the fluid.

The role of platelets in hemostasis and thrombosis requires that they become irreversibly attached at a site of injury; this occurs against the tendency of flow to move adhering platelets with the layer of blood adjacent to the surface. The force opposing a stable adhesion and aggregation is greater with an increasing shear rate; consequently, it can be surmised that shear-dependent phenomena are of particular relevance in those districts of the vasculature where shear forces are greater, that is, in arteries more than in veins and, particularly, in arterioles and capillaries. Moreover, in the presence of partial obstructions of the vessel lumen, as may be caused by atherosclerotic plaques, vasospasm, or both, fluid shear stress may increase considerably above the time average level of about 20 dynes per cm^2 calculated for the circulation of blood in normal vessels. The influence of shear-dependent phenomena, therefore, may be greater in

disorders that predispose to the occurrence of acute arterial occlusion than it is in the course of normal hemostasis.

The processes of platelet adhesion and aggregation offer several possible points of intervention for antithrombotic therapy. Those most actively evaluated for the development of new drugs involve adhesion receptors. As just outlined, during the initial response of platelets to vascular injury, there may be considerable differences between normal hemostasis and pathologic thrombosis. Indeed, the nature of the thrombogenic surfaces is likely to be different, as the composition of a ruptured atherosclerotic plaque does not resemble normal tissue exposed after trauma. Moreover, the presence of stenosis and the occurrence of abnormal vasospasm generate hemodynamic conditions that may be uniquely different from those prevailing in the normal circulation. It appears, then, that pathways particularly susceptible to the influence of shear stress, like those depending on von Willebrand factor and platelet glycoprotein Ib, should be an obvious target in a strategy aimed at blocking thrombosis without obliterating normal hemostatic responses. Perhaps the local inhibition of thrombin, an agonist that may be generated in excess in vascular lesions, may achieve the same result. The selective blockade of the glycoprotein IIb-IIIa complex, the key receptor involved in aggregation, should also prove useful, particularly if ligand-specific inhibitors will become available. A differential inhibition of fibrinogen and von Willebrand factor binding to glycoprotein IIb-IIIa, for example, should allow the antiplatelet intervention to be modulated and favor the blockade of high shear-dependent pathways, most likely involving von Willebrand factor. Thus, on the basis of ongoing research on pathophysiologic mechanisms, progress should be forthcoming in identifying selective inhibitors of specific adhesive interactions. Whether and how this will provide new and better antithrombotic drugs remain a challenge for the future on which many investigators are working today.

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Indications for Surgery in Necrotizing Pancreatitis

ANY DISCUSSION OF operative indications in severe acute pancreatitis must consider the need for an objective assessment of its severity in each patient. Such an assessment provides information about the prognosis, and this usually influences the clinical management—placement of the patient into an intensive care unit, the prophylactic use of antibiotics, and the like. In addition, some have suggested that if a specific level of severity is exceeded, this in itself could be an indication for operation.

Several prognostic scoring systems have been applied to acute pancreatitis in an effort to identify those patients who might benefit from more aggressive therapy. The Ranson system described in Frey's article in this issue of the journal has been used widely.[1,2] A number of modifications have been reported, but all of them, as well as the Ranson approach, are cumbersome to use and have been validated only for the first 48 hours of the disease. Thus, their applicability is limited for most patients with severe pancreatitis whose disease evolves over several weeks or more.

The Acute Physiology and Chronic Health Evaluation (APACHE II) score has been shown to correlate with the degree of pancreatic necrosis and eventual morbidity.[3,4] For example, in patients with less than 30% necrosis, the average APACHE II score is 8.4, which rises to 12.2 or more if more than 50% necrosis is present.[3] Nevertheless, the APACHE II calculations are also cumbersome and require a computer for effective application.

Computed tomography (CT) with a rapidly infused contrast medium provides the most accurate information about the adequacy of pancreatic perfusion and the presence of pancreatic necrosis, which correlates well with the prognosis.[5] We agree with Frey that it is the most valuable study in the management of this group of patients and that it provides information that is often critical in decisions about overall management, including whether to intervene surgically. A CT scan is indicated in patients who appear clinically to have severe pancreatitis or when there is no improvement with standard medical treatment after 48 to 72 hours. It should also be done in patients with a protracted clinical course to their disease or those in whom there is a change in condition that suggests a complication. The subject has been reviewed recently.[6]

Balthazar and co-workers have graded pancreatitis according to information derived from a CT scan about the degree of pancreatic enlargement, inflammation, and the presence of fluid collections.[7] They suggested that these data could be combined with information from the contrast-enhanced CT scan to create a CT severity index. In their experience, if the score was less than 2, the morbidity rate was 4% and no patients died. If the score was between 7 and 10, the morbidity rate was 92% and the death rate was 17%. This approach may deserve additional evaluation, but there is no evidence that it is better than existing methods (APACHE II, contrast-enhanced CT alone) for assessing severity.

Indications for Surgical Therapy

Many authors have used imprecise terms to describe their indications for surgical intervention in severe acute pancreatitis—such as sepsis, pain, anorexia, fever, mass effect, phlegmon, pancreatic abscess. The term "sepsis" is vague and undefined. There is general agreement that the term "phlegmon" should be eliminated. The term "pancreatic abscess" has been used wrongly to describe all types of pancreatic infection. This practice has made it

impossible to compare and contrast the experience from different centers and to arrive at a consensus about some of the indications.

We briefly describe our current indications for surgical intervention in patients with severe acute pancreatitis. Some are generally accepted; others are more controversial and the subject of continuing debate.

Differential Diagnosis

Today the diagnosis is unclear in only about 5% of cases of acute pancreatitis, and other intra-abdominal conditions—perforated duodenal ulcer, gangrenous cholecystitis, bowel obstruction—are seriously considered.[8,9] Because each of these requires surgical intervention, the pancreatitis is discovered at operation. Although diagnostic laparotomy does not exacerbate the pancreatitis, it may increase the incidence of subsequent pancreatic infection in patients with severe pancreatitis.[8] This is considered to be an acceptable risk, however, because a delay in the diagnosis and treatment of one of the other abdominal conditions mentioned could be catastrophic.

Biliary Pancreatitis

In patients with gallstones and mild acute pancreatitis, cholecystectomy should be done during the same hospital admission once the pancreatitis has resolved.[9] A recent study suggested that early (<24 hours) endoscopic stone extraction or sphincterotomy (or both) benefited patients with even mild biliary pancreatitis.[10] We remain skeptical that any intervention is indicated in these patients because almost all have spontaneous resolution of their symptoms. In those few patients with severe biliary pancreatitis and persistent signs and symptoms, or if cholangitis is present, endoscopic or surgical relief of the biliary obstruction is indicated within the first 48 hours. We prefer an endoscopic approach if skilled personnel are available.

Infected Pancreatic Necrosis

The presence of infected pancreatic necrosis is an undisputed indication for surgical intervention in patients with acute pancreatitis. Poorly enhanced pancreatic tissue as shown by contrast-enhanced CT scan correlates well with the presence of pancreatic necrosis.[6] Bacterial contamination of the necrotic pancreas occurs in as many as 70% of cases, and if gas bubbles are seen in the region of the pancreas on the scan, infection may be presumed to be present. Otherwise, local fluid or necrotic tissue should be aspirated percutaneously and Gram's stain and culture done. Because it has been documented that at least 50% of patients with infection may not show clinical sepsis, such as fever or leukocytosis, we generally aspirate in all patients who have undergone a CT scan in whom fluid is present. If infection is proved, an operation is indicated. Aspiration is safe, and the chances of missing an infection as a result of sampling error are low.[11] If unable to prove infection, we would repeat the CT scan and aspiration at weekly intervals. Deterioration in a patient's condition might require earlier aspiration or even an operation, however.

In this issue of the journal, Frey rightly stresses that patients with infected pancreatic necrosis require surgical debridement and drainage of the infection. Nonoperative methods such as the percutaneous placement of drains by radiologic techniques are doomed to failure because the thick particulate nature of the infected material rapidly plugs these drains.

Pancreatic Abscess

Pancreatic abscesses should be distinguished from infected pancreatic necrosis in that little or no necrotic material is present. They also typically appear later in the course of pancreatitis, often four weeks or more after the start of the attack. The diagnosis can be made with CT scan and percutaneous aspiration of the infected fluid. Because the pus usually contains little particulate material, our experience has been that percutaneous drainage is often effective and surgical drainage is usually not necessary. If, however, the septic clinical condition is not reversed rapidly after a percutaneous drain is placed, an operation should be done promptly.

Sterile Pancreatic Necrosis

Whether to operate on patients with sterile pancreatic necrosis is controversial. Beger and colleagues found that the extent of pancreatic necrosis influenced the mortality rate. When less than 30% of the gland was necrotic, 7% of their patients died. When all of the gland was necrotic, the mortality was 50%. Moreover, the likelihood of bacterial contamination was directly related to the degree of pancreatic necrosis.[12,13] When the extent of necrosis was 30%, 29% of the patients were infected. When the necrosis involved more than 50% of the gland, 71% of the patients were infected. Based on such data, these authors believe that operation is indicated in most patients with more than 50% gland necrosis as demonstrated on contrast-enhanced CT scan.

Other surgeons try to avoid an operation in patients with sterile pancreatic necrosis, regardless of its extent. They reason that an operation can be done if infection supervenes and that the available techniques for proving infection are safe and reliable. Bradley and associates have observed that many such patients recover without surgical intervention; others have had a similar experience.[14,15] Currently we use this approach for our patients, and there is no evidence that the outcome is any different with this more conservative method.

Persistent Disease, Deteriorating Clinical Course, and Organ System Failure

Some patients with sterile pancreatic necrosis will fail to improve with maximal nonoperative treatment. They may have persistent fever, abdominal pain, and an inability to eat. Computed tomographic scans may reveal an edematous and swollen pancreas, with or without fluid collections. Others deteriorate clinically despite their intensive care, often with failure of one or more organ systems. Both of these groups deserve serious consideration for operative intervention. The logic for operation in-

cludes the possibility that infection is present, but that it has been impossible to prove it with nonoperative techniques. It may also be that even without infection, the pancreas continues to release various poorly defined "toxic" substances, such as enzymes or vasoactive substances, whose drainage would benefit the patient. Finally, in rare cases a patient may have ductal obstruction that continues to exacerbate the inflammation.

In the presence of a mechanical cause for the pancreatitis, such as pancreatic duct stricture, an operation should be done promptly. In its absence, it is unclear how long to wait before an operation is undertaken. With stable but persistent disease and no organ system failure, we usually wait several weeks, with the hope that improvement will occur and an operation can be avoided. With a deteriorating course, and especially with one or more organ systems failing, we often operate within a few days. Nevertheless, because as many as 25% of patients recover from pulmonary, renal, or cardiovascular dysfunction without surgical therapy, it must be admitted that absolute criteria for an operation are lacking in these patients.[16]

Can the Decision to Operate Be Made More Objective?

It has been suggested that limits be set in terms of specific indicators of severity and that surgical therapy be undertaken when these are exceeded. For example, an operation might be done if the APACHE II score was greater than 12 or if the CT severity index (Balthazar) was more than 7. We are skeptical that this "cookbook" approach to clinical decision making is better than the judgment of an experienced surgeon.

As more organ systems fail, the mortality rate rises.[17-19] This is true for many diseases in addition to pancreatitis. In a group of patients with severe pancreatitis, the survivors had an average of 1.4 organ systems involved; those who died had 3.2. In Büchler and associates' patients, pulmonary insufficiency occurred in 24% of those with sterile necrosis and about half of those with infected necrosis. Renal insufficiency and shock were also seen in 20% to 30% of cases (Table 1).[16] Thus, there has been a tendency to intervene surgically when organ systems begin to fail and when they remain unresponsive to the usual medical measures. Of course, we do not know whether surgical intervention is responsible for the reversal in organ system deterioration that is sometimes seen. This question needs to be studied prospectively.

Surgical Principles

Extensive debridement of necrotic pancreatic and peripancreatic tissue is the cornerstone of surgical management. Infected tissues should be debrided, fluid evacuated, and the areas irrigated copiously. Viable pancreas should not be removed. We also place a feeding jejunostomy tube in most of these critically ill patients. Even if all of the patient's caloric needs cannot be supplied this way, it is important to maintain the integrity of the gut mucosa by providing luminal nutrients. There is evidence from patients with other critical illnesses that this decreases the incidence of bacterial translocation and may prevent the "sepsis syndrome."[17,18,20]

TABLE 1.—*Incidence of Organ Failure and Clinical Sepsis in 134 Patients With Acute Necrotizing Pancreatitis**

	Necrotic Pancreatitis			
	Infected Patients (n = 55)		Sterile Patients (n = 79)	
Complication	No.	%	No.	%
Pulmonary insufficiency†	27	49	19	24
Renal insufficiency‡	18	33	15	19
Shock§	12	22	6	8
Sepsis‖	27	49	9	11

*Modified from Büchler et al.[16] Note that only half of the patients with infection were clinically septic and that 11% of patients with sterile necrosis had evidence of sepsis.

†Po_2 <60 torr.

‡Serum creatinine level >120 μmol per liter.

§Systolic blood pressure <80 mm of mercury for >15 minutes.

‖Temperature >38.5°C; leukocyte count <4 × 10^9 per liter (4,000 per μl) to >12 × 10^9 per liter (12,000 per μl); platelet count <1.5 × 10^9 per liter (<150,000 per μl); metabolic acidosis >−4 mmol per liter.

There has been discussion about the merits of "closed" versus "open" techniques of drainage. Büchler and coworkers have popularized the closed approach in which postoperative lesser sac lavage is accomplished through large drains placed at the time of the operation.[16] The abdominal incision is closed, and there is no planned reexploration. The open approach has been promulgated by Bradley and well described by Frey.[1,21] Because the results from both approaches appear to be equivalent, we usually use the closed technique, which requires fewer resources and is simpler. In patients with extensive necrosis where effective postoperative lavage may not be possible, we agree with Frey that the open technique may be better. Even with the closed technique, reoperation is required in as many as 30% of patients, usually for recurrent or persistent infection and occasionally for hemorrhage.[16]

Summary

The decision to operate on a patient with severe acute pancreatitis is often difficult and requires mature clinical judgment. Indications that are widely accepted include to establish the differential diagnosis, when the surgeon is concerned that the symptoms are due to a disease other than pancreatitis for which an operation is mandatory; in persistent and severe biliary pancreatitis, when an obstructing gallstone is lodged in the ampulla of Vater and cannot be managed endoscopically; in the presence of infected pancreatic necrosis; and to drain a pancreatic abscess, if percutaneous drainage does not produce the desired result. Other indications that are less well defined and somewhat controversial are the presence of sterile pancreatic necrosis involving 50% or more of the pancreas, when the pancreatitis persists despite maximal medical therapy, and when a patient's condition deteriorates. For these last three indications, guidelines have been presented that permit a logical approach to management, although uncertainty remains. Surgeons should strive to describe in detail and precisely the clinical state

of their patients at the time that an operation is done, as well as the findings and technical details of the operation. This should allow further refinement in the management of this vexing problem.

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More on Mountain Biking

To the Editor: The recent article by Chow, Bracker, and Patrick[1] makes a timely contribution to the medical literature on bicycling. In the past decade the specific health hazards that accompany mountain bicycling (also known as ATB—all-terrain bicycle) were either not reported or were hidden in generic "bicycle" articles.[2] My own experience and a review of sports medicine publications suggest that pelvic fractures in particular occur at a notable rate.

In 1993 I fractured my pelvis and acetabulum in a fall from my mountain bicycle. During my recovery I was introduced to two other mountain bicycle enthusiasts who had themselves incurred similar injuries just months before. Casual investigation among their acquaintances and my interview of physician colleagues have brought to my attention no fewer than six other recent serious pelvic fractures sustained during mountain bicycling in the southern California area alone. Bob Howells, mountain bicycle expert, journalist, and pelvic fracture victim, succinctly described our plight in his observation, "We have no helmets for our hips" (Bob Howells, personal communication, May 1993).

Apparently when a young mountain bicyclist falls directly on the greater trochanter, even at moderate speeds, the dense femoral head is likely to punch through the acetabulum, creating a fracture more often associated with head-on automobile collisions or falls from great heights. Physicians facing this injury need to be familiar with the literature that establishes aggressive surgical repair by experienced hands as the appropriate, and possibly critical, approach required to achieve the best result.[3,4]

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* * *

Dr Chow Responds

To the Editor: I agree with Dr Barnett that the specific hazards of off-road bicycling have probably been "hidden in generic bicycle articles." In addition, I think information regarding all-terrain bicycles (ATBs) is hidden in medical diagnoses that identify the cause of these hazards as generic bicycle accidents. Many of us who are mountain bike enthusiasts have our own impression of risks in this sport, which are based on personal experiences and anecdotal cases. Barnett's unfortunate mishap has put him into contact with others with similar injuries from the sport and, thus, a bias has resulted. The incidence of serious pelvic fractures from mountain biking is unknown.

My experiences have been different, and I also have my own bias. In our investigation,[1] most accidents occurred while going downhill. This exposes the rider to a vulnerable posture, with a tendency for the rider to become "launched" over the handlebars. The head often strikes the ground, and although most ATB riders wear helmets, conventional bicycle helmets may be inadequate in a sport that has progressed to a level beyond what was anticipated when equipment was designed. Many riders strike their unprotected face, and massive facial trauma occurs. The cervical spine is unprotected, and the potential for serious injury exists. As in pelvic fractures, the specific details of head and neck trauma are not certain.

The next logical step in our efforts to learn more about injury patterns in off-road cycling is a prospective analysis of accidents in which the rider seeks medical attention. This sounds simple, but the difficulty lies in finding a suitable medical facility where the incidence of these mishaps will allow a population of substantial size to be studied. An investigation of this type would greatly enhance our knowledge and help our goal of making this sport as safe as possible.

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Human Immunodeficiency Virus and Primary Pulmonary Hypertension

To the Editor: Primary pulmonary hypertension is a disease of unknown cause.[1] A close association with human immunodeficiency virus (HIV) disease has been reported only recently.[2] The purpose of this report is to document another case of progressive primary pulmonary hypertension in a young woman seropositive for HIV infection.

Report of a Case

The patient, a 38-year-old woman, was seen because for four months she had had progressive dyspnea on exertion, pedal edema, and abdominal distension. Her medical history was remarkable for adequately controlled hypertension, and she recently tested positive for HIV antibody. The patient admitted to having abused drugs 20 years ago.

On physical examination she had mild tachycardia, tachypnea, jugular venous distension, hepatojugular reflux, bilateral pitting edema, left parasternal heave, an accentuated second heart sound with P_2 being louder than A_2, a murmur of tricuspid regurgitation, tender hepat-

omegaly, and moderate ascites. There was no clinical evidence of connective tissue disease, vasculitis, or hemoglobinopathy. Radiographic examination of the chest revealed borderline cardiomegaly. An electrocardiogram showed a normal sinus rhythm and right ventricular hypertrophy. At echocardiography she had right ventricular dilatation and hypertrophy with tricuspid regurgitation and mild global hypokinesia, with a left ventricular ejection fraction of 47%.

A lung scan failed to reveal any ventilation-perfusion abnormalities. Cardiac catheterization showed systolic and end-diastolic right ventricular pressures of 72 and 21 mm of mercury, respectively. The mean pulmonary capillary wedge pressure was 6.7 mm of mercury. The calculated pulmonary vascular resistance was 1,943 dynes per second per cm^2 (normal, 20 to 130). There was no oxygen step-up suggestive of intracardiac shunt. A diagnosis of primary pulmonary hypertension was established when the diagnostic workup following the guidelines established by the National Institutes of Health registry for primary pulmonary hypertension failed to identify a specific cause for the patient's pulmonary hypertension. The patient refused a lung biopsy. Eight months after the diagnosis the patient is alive although her respiratory distress is progressing slowly.

Primary pulmonary hypertension with necrotizing arteritis[3,4] and plexogenic arteropathy[3-5] have been reported recently in persons with HIV infection. Attempts to identify virus in the pulmonary vascular endothelium of these patients have not been successful.[6] It is speculated that the vascular lesions are either due to an unusual immune response to the HIV[3,4] or are mediated by some growth factor associated with it.[6] As a result, testing for HIV infection in all patients with primary pulmonary hypertension has been recommended.[2-6] Most cases reported so far (about 25) had presentations similar to this case, with a few months' history of dyspnea and fatigue preceding the diagnosis and the rapid deterioration of symptoms thereafter. Numerous cardiopulmonary manifestations of the acquired immunodeficiency syndrome have been reported.[7] Apart from lung infections, dilated cardiomyopathy, pericardial effusion, and pleural effusion are the other common cardiopulmonary lesions in patients with HIV disease.

The few reports published of patients infected with HIV in whom findings consistent with primary pulmonary hypertension have developed suggest a link between a viral infection and pulmonary hypertension. It is advisable that this association be considered while evaluating unexplained dyspnea in HIV-positive patients, and HIV testing should be done in all patients with primary pulmonary hypertension.

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The Editors are pleased to receive letters commenting on articles published in the journal in the past six months, as well as information or short case reports of interest to our readers. ALL MATERIAL SUBMITTED FOR CONSIDERATION MUST BE DOUBLE-SPACED. Letters NO LONGER THAN 500 WORDS are preferred. An original typescript and one copy should be submitted. All letters are published at the discretion of the Editors and subject to appropriate editing. Those of a scientific nature will be peer reviewed. Authors should include information regarding conflict of interest, when appropriate ("I warrant that I have no financial interest in the drugs, devices, or procedures described in this letter"). Most letters regarding a previously published article will be sent to the authors of the article for comment. Authors of accepted letters will have an opportunity to review the edited version before publication.

Lessons From the Practice

Comadre Padre

ALLAN L. McCALL, Sr, MD, *Redlands, California*

The telephone call came at 2 AM. Having just entered general practice, I was answering every call. "This is Pauline," she said, as though I should attach special importance to that. "I have a child with croup who must have help." The address was a small *barrio* nestled in the curve of a railroad track. When I arrived Pauline was waiting with a flashlight to guide me into a shack where a toddler did, indeed, have inspiratory stridor. Pauline had already prepared a crude steam tent with bedsheets, clothespins, and hot water. Because of my poor Spanish, she acted as interpreter for the parents while I completed the history, examination, and treatment.

I came to learn that she was considered *comadre* by the small community and was most often the first one called in cases of sickness or disaster. Although not formally trained, she had a good knowledge of simple nursing procedures and had an uncanny ability to obtain help for her little realm whether or not there was money to pay for it. Over the ensuing years she called me periodically for an amazing variety of problems—wounds, precipitous home births, abused women, spontaneous and induced abortions, and overdoses.

After one such nocturnal problem had been attended to, she took me aside and requested medication for herself because she could not sleep. It became quickly obvious that her insomnia was actually orthopnea. She had classic Corrigan carotid pulsations, and her nail beds showed capillary pulsation. Yes, she had had *reumatismo* as a child. Yes, her feet were swollen, even in the morning. I gave her a dose of digitalis and a mercurial diuretic injection and instructed her about diet and fluid intake.

As the years passed her condition fluctuated. The new thiazide diuretics gave her a prolonged improvement. Ultimately, she was referred for valvular repair, but this gave only transient relief. Then a telephone call came. "Pauline wants you to come see her," the voice said. I explained that I had been retired for five years and could not help her. "She doesn't need medical help," the voice said. "She is dying and has had last rites. She knows she is beyond help but wants to see you."

When I entered her home, the shades were drawn, the candles were lit, and a dozen relatives stood solemnly around the room. An emaciated Pauline sat in the center of the room. Her respirations were noisy, and she was struggling for each breath. As she saw me her eyes seemed to clear, and I knelt to give her a hug. She turned to the relatives and said, "This is an old-time doctor. He doesn't need x-rays to know what's wrong with you. He can look at your neck and fingernails and know all about you." A scant few sentences later she began to tire. "I must go now, Pauline. I am tiring you," I said. As I stood her eyes clouded again. She took my hand and said, "Thank you for coming to see me, Father."

* * *

"Lessons From the Practice" presents a personal experience of practicing physicians, residents, and medical students that made a lasting impression on the author. These pieces will speak to the art of medicine and to the primary goals of medical practice—to heal and to care for others. Physicians interested in contributing to the series are encouraged to submit their "lessons" to the series' editors.

JONATHAN E. RODNICK, MD
STEPHEN J. McPHEE, MD
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(McCall AL Sr: Comadre padre. West J Med 1993; 159:710)

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Why Physicians Retire Continued (Correspondence), Alex Milyko ..... (Oct) 512

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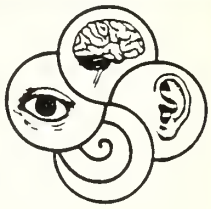

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Jean-Marie Aran
Robert Baloh
Donald Becker
Andreas Bohmer
Bernard Cohen
Joseph Demer
John Epley
Ugo Fisch
Joseph Furman
Jeffrey Harris
Vicente Honrubia
Kathleen Horner
Herman Jenkins
David Lim
Brenda Lonsbury-Martin
Paul Micevych
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Joseph Nadol
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For further information and applications for registration and poster presentation, contact:
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Clinical Applications of Vestibular Science
15-50 Rehabilitation Center
UCLA
Los Angeles, CA 90024
Phone (310)825-5131
FAX: (310)206-2327

CONTINUING MEDICAL EDUCATION

(Continued from Page 656)

February 17-19—**Recent Advances in Neurology.** UCSF at Sheraton Palace Hotel, San Francisco. Thurs-Sat. 15 hrs. $355. Contact: UCSF.

February 19-24—**Topics and Advances in Internal Medicine.** UCSD at San Diego Marriott Hotel, San Diego. Sat-Thurs. 52 hrs. $595. Contact: UCSD.

February 26-27—**Endoscopy 1994.** Southern California Society for Gastrointestinal Endoscopy at Century Plaza Hotel, Los Angeles. Sat-Sun. Contact: Joyce M. Fried, 10833 Le Conte Ave, Los Angeles 90024-1722. (310) 374-9708.

March 4—**20th Annual Diabetes Symposium.** UCD at Sheraton Sunrise Hotel, Sacramento. Fri. 6 hrs. $130. Contact: UCD.

March 18-24—**Internal Medicine: 1994.** Sharp Memorial Hospital at Hotel del Coronado, San Diego. Fri-Thurs. 54 hrs. $695. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

OB/GYN

January 14—**OB/GYN Symposium.** San Jose Medical Center. Fri. 6 hrs. Contact: Theresa Goodnight, (408) 977-4490.

January 16-18—**Ambulatory Obstetrics and Gynecology.** UCD at Hyatt Regency Lake Tahoe, Incline Village, Nevada. Sun-Tues. 14.5 hrs. $300-$375. Contact: UCD.

March 19—**Health Care Issues for Women Over 40.** California Medical Association's Western Scientific Assembly at Disneyland Hotel, Anaheim. Sat. 3.5 hrs. Contact: Arlene Sirott, (415) 882-3384.

April 20-24—**Pacific Coast Fertility Society Annual Scientific Program and Postgraduate Course.** Pacific Coast Fertility Society at Stouffer Esmeralda Resort, Indian Wells. Wed-Sun. 17 hrs. Contact: Director, Continuing Medical Education, 15731 Imperial Hwy, Ste 427, La Mirada 90638-2510. (310) 947-7068.

OCCUPATIONAL/ENVIRONMENTAL

January 31-February 4—**Occupational and Environmental Medicine.** UCSF at Miyako Hotel, San Francisco. Mon-Fri. Contact: UCSF.

March 19—**Practical Aspects of Occupational Medicine.** California Medical Association's Western Scientific Assembly at Disneyland Hotel, Anaheim. Sat. 4 hrs. Contact: Arlene Sirott, (415) 882-3384.

ONCOLOGY

January 28-30—**46th Annual Midwinter Oncology Conference.** Los Angeles Radiological Society at Century Plaza Hotel, Los Angeles. Fri-Sun. 16.5 hrs. $450. Contact: LARS, PO Box 91215, Los Angeles 90009-1215. (310) 827-9078 or (800) 527-7013.

February 21-23—**Clinical Hematology and Oncology: 1994.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Mon-Wed. 18 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

OPHTHALMOLOGY

January 29—**General Medicine Update for the Ophthalmologist.** UCD at Cancer Center Auditorium, Sacramento. 6 hrs. $95. Contact: UCD.

March 20—**Ophthalmologist-Gatekeeper Interactions: Managed Eye Care.** California Medical Association's Western Scientific Assembly at Disneyland Hotel, Anaheim. Sun. 3.5 hrs. Contact: Arlene Sirott, (415) 882-3384.

May 21—**Pearls of Ocular Therapy.** Scripps Clinic and Research Foundation at La Jolla. Sat. 8 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

ORTHOPEDICS

January 20-23—**Reconstruction of the Adult Hip: A Comprehensive Course.** American Academy of Orthopedic Surgeons at Hyatt Regency Maui, Lahaina, Hawaii. Thurs-Sun. Contact: AAOS, 6300 N River Rd, Rosemont, IL 60018-4262. (708) 823-7186.

January 23-26—**Fracture Management.** UCD at Resort at Squaw Creek, Squaw Valley. Sun-Wed. 15 hrs. $495. Contact: UCD.

January 27-30—**Spring Meeting of the Northern California Chapter of the Western Orthopedic Association** at Inn at Squaw Creek, Olympic Valley. Thurs-Sun. Contact: Iola Beckley, (707) 538-5548.

March 20—**Musculoskeletal Trauma in Children and Adolescents.** California Medical Association's Western Scientific Assembly at Disneyland Hotel, Anaheim. Sun. 3.5 hrs. Contact: Arlene Sirott, (415) 882-3384.

1993-1994—**Educational Program for Musculoskeletal Evaluation and Rehabilitation.** UCSD at La Jolla. 35.5 hrs. $500. Contact: UCSD.

OTOLARYNGOLOGY

January 16-21 and February 13-18—**Temporal Bone Dissection Course.** House Ear Institute. Sun-Fri. 53 hrs. $875-$1,100. Contact: Antonio De la Cruz, 2100 W Third St, Los Angeles 90057. (213) 483-4431 ext. 7079.

March 18—**Pediatric Otolaryngology: What Gatekeepers Need to Know.** California Medical Association's Western Scientific Assembly at Disneyland Hotel, Anaheim. Fri. 4 hrs. Contact: Arlene Sirott, (415) 882-3384.

April 6-8—**Temporomandibular Joint Update.** UCD at Silverado Resort, Napa. Wed-Fri. 12 hrs. $300. Contact: UCD.

PATHOLOGY

March 18—**Skin Cancer: A Clinical and Histopathologic Update.** California Medical Association's Western Scientific Assembly at Disneyland Hotel, Anaheim. Fri. 3 hrs. Contact: Arlene Sirott, (415) 882-3384.

April 16—**New Treatments in Chronic Liver Disease.** Scripps Clinic and Research Foundation at La Jolla. Fri. 6 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Blvd, La Jolla 92037. (619) 554-8556.

May 26-28—**10th Annual Current Issues in Anatomic Pathology.** UCSF at San Francisco. Thurs-Sat. Contact: UCSF.

PEDIATRICS

January 24-28—**San Diego Conference on Responding to Child Maltreatment.** Children's Hospital San Diego at Town and Country Hotel, San Diego. Mon-Fri. $390. Contact: Center for Child Protection, 8001 Frost St, San Diego 92123. (619) 395-4950.

February 21-23—**Pediatrics Update 1994.** San Diego State University at Hyatt Islandia, San Diego. Mon-Wed. 20 hrs. $450. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2297.

March 19—**Pediatrics Emergencies.** California Medical Association's Western Scientific Assembly at Disneyland Hotel, Anaheim. Sat. 4 hrs. Contact: Arlene Sirott, (415) 882-3384.

May 12-14—**27th Annual Advances and Controversies in Clinical Pediatrics.** UCSF at San Francisco. Thurs-Sat. Contact: UCSF.

PSYCHIATRY

January 23-28—**20th Annual Midwinter Program in Continuing Medical Education for Psychiatrists.** UCD at Hyatt Regency Lake Tahoe, Incline Village, Nevada. Sun-Fri. 25 hrs. $395. Contact: UCD.

February 18-20—**West Coast Psychiatry Board Review: Preparation for Part II.** UCSD at Hyatt Regency, La Jolla. Fri-Sun. 16 hrs. $475. Contact: UCSD.

February 26—**1994 Sleep Medicine Update.** Scripps Clinic and Research Foundation at La Jolla. Sat. 7 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

March 5, 6, 19, 20—**Introductory Workshop in Clinical Hypnosis for Physicians, Dentists and Psychologists.** San Francisco Academy of Hypnosis at Alta Bates Hospital, Berkeley. Sat-Sun. 28 hrs. $375. Contact: San Francisco Academy of Hypnosis, Verna Carter, 29 Pinto Ave, San Francisco 94132. (415) 239-4104.

1993-1994—**Basic Clinical Hypnosis Training.** UCSD at La Jolla. Ongoing. 30 hrs. $245. Contact: UCSD.

RADIOLOGY

January 17-19—**Neuroradiology Update.** Stanford University Medical Center at Ritz-Carlton, Laguna Niguel. Mon-Wed. 17.5 hrs. $450. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

January 20-23—**Breast Imaging Update.** Stanford University Medical Center at Ritz-Carlton Hotel, Laguna Niguel. Thurs-Sun. 16 hrs. $450. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

February 14-18—**Magnetic Resonance Imaging.** UCSD at Hotel del Coronado, San Diego. Mon-Fri. 30 hrs. $425. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

February 21-25—**Contemporary Diagnostic Imaging.** Stanford University Medical Center at Ritz-Carlton Resort Hotel, Kapalua, Hawaii. Mon-Fri. 20.5 hrs. $550. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925.

(Continued on Page 726)

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(Continued from Page 645)

SAWYER, WILLIAM C., San Francisco. Died Aug 16, 1993, aged 73. Graduate of University of Oklahoma College of Medicine, Oklahoma City, 1951. Licensed in California in 1954. Dr Sawyer was a member of the San Francisco Medical Society.

SHEPHERD, GARY LEE, San Diego. Died May 20, 1993, aged 54. Graduate of University of Oklahoma College of Medicine, Oklahoma City, 1965. Licensed in California in 1969. Dr Shepherd was a member of the San Diego County Medical Society.

SPENCER, JAMES R., Jr, Templeton. Died Oct 21, 1993, aged 78. Graduate of University of Texas Medical Branch, Galveston, 1944. Licensed in California in 1946. Dr Spencer was a member of the San Luis Obispo County Medical Society.

STOCKER, HOWARD O., San Bernardino. Died May 25, 1993, aged 79. Graduate of Loma Linda University School of Medicine, 1938. Licensed in California in 1939. Dr Stocker was a member of the San Bernardino County Medical Society.

ULDALL, JORGEN J., San Francisco. Died Aug 29, 1993, aged 81. Graduate of Creighton University School of Medicine, Omaha, Nebraska, 1938. Licensed in California in 1939. Dr Uldall was a member of the San Francisco Medical Society.

WAITES, LARRY A., San Francisco. Died Jul 20, 1993, aged 43. Graduate of Medical College of Georgia, Augusta, 1976. Licensed in California in 1977. Dr Waites was a member of the San Francisco Medical Society.

WATSON, CHARLES M., San Francisco. Died Jul 17, 1993, aged 55. Graduate of Wayne State University School of Medicine, Detroit, Michigan, 1964. Licensed in California in 1968. Dr Watson was a member of the San Francisco Medical Society.

WILBUR, MARK JEFFREY, Sunnyvale. Died Sep 30, 1993, aged 39. Graduate of University of California, Irvine, California College of Medicine, 1980. Licensed in California in 1981. Dr Wilbur was a member of the Santa Clara County Medical Association.

YOUNG, FORREST, Redlands. Died Sep 16, 1993, aged 87. Graduate of Stanford University School of Medicine, Stanford, California, 1931. Licensed in California in 1947. Dr Young was a member of the San Bernardino County Medical Society.

Denver Medical Society

BOWLING, FRANKLIN LEE. Died Jul 13, 1993, aged 83. Graduate of University of Colorado School of Medicine, Denver, 1946. Licensed in Colorado in 1946.

MITCHELL, ROGER SHERMAN. Died Sep 1, 1993, aged 85. Graduate of Harvard Medical School, 1934. Licensed in Colorado in 1955.

RIDER, MITCHELL BURNS. Died Jun 22, 1993, aged 72. Graduate of University of Colorado School of Medicine, Denver, 1946. Licensed in Colorado in 1946.

SLAGLE, DEROY WILLIAM HARTLEY. Died May 25, 1993, aged 77. Graduate of University of Colorado School of Medicine, Denver, 1942. Licensed in Colorado in 1942.

(Continued from Page 724)

March 7-10—**Magnetic Resonance Imaging.** UCSD at Hotel del Coronado, San Diego. Mon-Thurs. 30 hrs. $625. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

March 19—**Dilemmas in Women's Imaging.** California Medical Association's Western Scientific Assembly at Disneyland Hotel, Anaheim. Sat. 4 hrs. Contact: Arlene Sirott. (415) 882-3384.

March 20-25—**UCLA General Radiology Review Course.** UCLA at Doubletree Hotel, Marina Del Rey. Sun-Fri. 40 hrs. $400. Contact: UCLA.

March 21-26—**Musculoskeletal and Neuro MRI.** UCSD at La Costa Resort and Health Spa, Carlsbad. Mon-Sat. 19.5 hrs. $550. Contact: UCSD.

April 3-8—**14th Annual Residents Radiology Review Course.** UCSD at Hotel Del Coronado, San Diego. Sun-Fri. 41 hrs. $450. Contact: UCSD.

April 9—**Interventional Radiology.** UCSD at Hotel Del Coronado, San Diego. Sat. 8 hrs. $135. Contact: UCSD.

1993-1994—**Fellowship in Interventional Radiology for Radiologists.** UCSD Medical Center. Ongoing. 40 hrs. $700. Contact: UCSD.

1993-1994—**Visiting Fellowship in Magnetic Resonance Imaging.** UCSD at MR Institute, San Diego. Ongoing. 40 hrs. $1,200. Contact: UCSD.

1993-1994—**Visiting Fellowship for Physicians and Sonographers in Duplex Ultrasound: Focus on Carotid and Deep Venous Thrombosis.** Ongoing. 30 hrs. $600. Contact: UCSD.

1993-1994—**Visiting Fellowship Program of Endovaginal Sonography: Focus on Techniques and Application.** UCSD Medical Center. Monthly. 30 hrs. $600. Contact: UCSD.

SURGERY

January 14-15—**What's New in General Surgery.** UCD at Hyatt Regency Hotel, Sacramento. Fri-Sat. 15 hrs. $285. Contact: UCD.

March 24-25—**9th Annual Course in Colon and Rectal Surgery.** USC at Ritz-Carlton Huntington Hotel, Pasadena. Thurs-Fri. Contact: Donna Bowker, 1975 Zonal Ave, KAM 307, Los Angeles 90033. (213) 342-2555.

March 24-26—**6th Annual Symposium on Aesthetic Surgery of the Face.** UCSF at San Francisco. Thurs-Sat. Contact: UCSF.

GENERAL/MULTIDISCIPLINARY

January 7-9—**7th Annual Medical Office Laboratory Conference.** SDSU at Red Lion Hotel, San Diego. Fri-Sun. 20 hrs. $425. Contact: Nancy Geiser, (619) 594-6255.

January 27-30—**Medicine Meets Virtual Reality II: Interactive Technology and Healthcare: Visionary Applications for Simulation, Visualization and Robotics.** UCSD at San Diego Marriott & Marina. Thurs-Sun. 21 hrs. $390. Contact: UCSD.

February 6-11—**26th Annual CME/Ski Meeting.** Nevada Academy of Family Physicians at Harvey's Resort, Lake Tahoe. Sun-Fri. 39 hrs. Contact: Debi Bradley, PO Box 7471, Reno, NV 89510. (702) 826-5100.

February 12-13—**Clinical Applications of Vestibular Science.** UCLA. Sat-Sun. $350. Contact: Marjorie Harris, 15-50 Rehabilitation Center, UCLA 90024. (310) 825-5131.

February 14-18—**5th Annual Physician Heal Thyself.** UCSD at Palm Springs Hilton. Mon-Fri. 16 hrs. $395. Contact: UCSD.

March 20—**Risk Issues in Cost Contained Care.** California Medical Association's Western Scientific Assembly at Disneyland Hotel, Anaheim. Sun. 3 hrs. Contact: Arlene Sirott. (415) 882-3384.

March 25-27—**63rd Clinical Conference.** Research Study Club at Huntington Ritz-Carlton Hotel, Pasadena. Fri-Sun. 15 hrs. Contact: Louise Ball, PO Box 1216, Murrieta 92564. (909) 677-4482.

HOME STUDY/SELF ASSESSMENT

Audio-Digest Foundation. California Medical Association. Contact: Audio-Digest Foundation, 1577 E Chevy Chase, Glendale 91206. (213) 245-8505.

COLORADO

This listing of continuing medical education programs in Colorado is compiled by the Denver Medical Society. To list CME programs here, please send information at least two months in advance to: Mr Robert L. Kennedy, Denver Medical Society, 1850 Williams Street, Denver, CO 80218; or telephone (303) 377-1850.

Brochures, course information, and registration forms are available from the contact person or organization.

December 18—**Computers in Medicine.** Rose Medical Center at Hotel L'Ostello, Vail. Sat. Repeated weekly through April 23, 1994, at either Hotel L'Ostello, Vail, or Hotel Wildwood, Snowmass Village. Contact: Bernard Karshmer, (800) 525-5810.

January 5-8—**Sports Medicine 1994.** American Academy of Orthopaedic Surgeons at Sheraton Steamboat, Steamboat Springs. Wed-Sat. Contact: AAOS Course Operations, (708) 823-7186.

January 20-23—**The Psychobiology of Hypnotic and Dissociative States.** American Psychiatric Association and Colorado Psychiatric Society at Sonnenalp Hotel, Vail. Thurs-Sun. Contact: Karen Spalter, (303) 759-6045.

January 22-29—**Reconstructive Surgery of the Hip and Knee.** University of Colorado School of Medicine at Sheraton at Steamboat, Steamboat Springs. Sat-Sat. Contact: U of Colo.

January 23-29—**Fifth Annual Geriatrics Overview/ Board Review.** University of Colorado School of Medicine at Beaver Run Resort, Breckenridge. Sun-Sat. Contact: U of Colo.

January 27-29—**Contemporary Management of Unstable Coronary Syndromes.** Department of Veterans Affairs and University of Colorado School of Medicine at Beaver Run Resort, Breckenridge. Thurs-Sat. Contact: Karen Babcock, (303) 393-2826.

January 29-February 5—**Internal Medicine Conference.** Rose Medical Center at Radisson Resort, Vail. Sat-Sat. Contact: Bernard Karshmer, (800) 525-5810.

February 4-5—**Ninth Annual Rocky Mountain HIV Disease Conference.** University of Colorado School of Medicine at the Red Lion, Denver. Fri-Sat. Contact: U of Colo.

February 5-12—**General Surgery Conference.** Rose Medical Center at Radisson Resort, Vail. Sat-Sat. Contact: Bernard Karshmer, (800) 525-5810.

February 12-19—**Emergency Medicine Conference.** Rose Medical Center at Radisson Resort, Vail. Sat-Sat. Contact: Bernard Karshmer, (800) 525-5810.

February 12-19—**Psychiatry Conference.** Rose Medical Center at Radisson Resort, Vail. Sat-Sat. Contact: Bernard Karshmer, (800) 525-5810.

February 19-26—**Neurology Conference.** Rose Medical Center at the Antlers Hotel, Vail. Sat-Sat. Contact: Bernard Karshmer, (800) 525-5810.

February 19-26—**Obstetrics and Gynecology Conference.** Rose Medical Center at Radisson Resort, Vail. Sat-Sat. Contact: Bernard Karshmer, (800) 525-5810.

February 26-March 3—**Horizons in Surgery.** University of Colorado School of Medicine at Beaver Run Resort, Breckenridge. Sat-Thurs. Contact: U of Colo.

February 26-March 4—**Crash '94 Colorado Review of Anesthesia.** University of Colorado School of Medicine at Radisson Resort, Vail. Sat-Fri. Contact: U of Colo.

February 26-March 5—**Pediatrics Conference.** Rose Medical Center at Radisson Resort, Vail. Sat-Sat. Contact: Bernard Karshmer, (800) 525-5810.

February 26-March 5—**Infectious Disease Conference.** Rose Medical Center at the Antlers Hotel, Vail. Sat-Sat. Contact: Bernard Karshmer, (800) 525-5810.

March 5-12—**Primary Care Conference.** Rose Medical Center at Radisson Resort, Vail. Sat-Sat. Contact: Bernard Karshmer, (800) 525-5810.

March 5-12—**Minding the Body/Mending the Mind.** Rose Medical Center at the Antlers Hotel, Vail. Sat-Sat. Contact: Bernard Karshmer, (800) 525-5810.

March 6-11—**14th Annual Keystone ENT Conference.** University of Nebraska Medical Center at Keystone Resort, Keystone. Sun-Fri. Contact: U of Nebraska Continuing Education Center, (402) 559-4152.

March 12-19—**Sports Medicine Conference.** Rose Medical Center at Radisson Resort, Vail. Sat-Sat. Contact: Bernard Karshmer, (800) 525-5810.

March 12-19—**Urology Conference.** Rose Medical Center at Radisson Resort, Vail. Sat-Sat. Contact: Bernard Karshmer, (800) 525-5810.

March 19-26—**Cancer Treatment Conference.** Rose Medical Center at the Antlers Hotel, Vail. Sat-Sat. Contact: Bernard Karshmer, (800) 525-5810.

Tuesday Noon Conferences—**Various Topics in Medicine.** Lutheran Medical Center, Wheat Ridge. Contact: Jean A. Kline, (303) 425-2951.

Every Second Wednesday of the Month—**Cardiovascular Education Series.** St Anthony Hospitals at St Anthony Hospital, Denver. Contact: Rose Powell, (303) 629-3678.

Every Friday (except 4th Friday of month)—**Various Topics in Contemporary Medicine (Midday CME Series).** St Anthony Hospitals at St Anthony Hospital, Denver. Contact: Rose Powell, (303) 629-3678.

First Wednesday of Each Month—**Various Topics in Neurology.** Sponsored by the Colorado Society of Clinical Neurologists. Contact: Colorado Society of Neurologists, (303) 449-3566.

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CONTINUING MEDICAL EDUCATION

(Continued from Page 726)

CONTACT INFORMATION

U of Colo—Contact: University of Colorado School of Medicine, Office of Continuing Medical Education, 4200 E 9th Ave, Denver, CO (303) 270-5195 or (800) 882-9153; FAX (303) 270-6761.

IDAHO

February 18-20—**Ada County Medical Society—35th Annual Medical Winter Clinics—An Anthology of Clinically Relevant Topics for All Physicians.** Shore Lodge Inn, McCall. Fri-Sun. 9 hrs. $125, Idaho Medical Society members; $175, nonmembers. Contact: Ada County Medical Society, PO Box 2668, Boise 83701. (208) 336-2930 or (208) 386-2135.

July 28-30—**Idaho Medical Association—Annual Meeting.** Sun Valley. Wed-Fri. Contact: IMA, 305 W. Jefferson, PO Box 2668, Boise 83701. (208) 344-7888.

NEW MEXICO

Information, requests for accreditation, and items to be listed should be sent to the chair of the CME Committee, New Mexico Medical Society, 7770 Jefferson, Suite 400, Albuquerque, NM 87109, at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 828-0237.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

(Continued on Page 728)

HOSPITAL BASED PHYSICIAN CONTRACTS

DISCUSSES the contract terms which may be contained in hospital based contracts, from a legal and practical standpoint.

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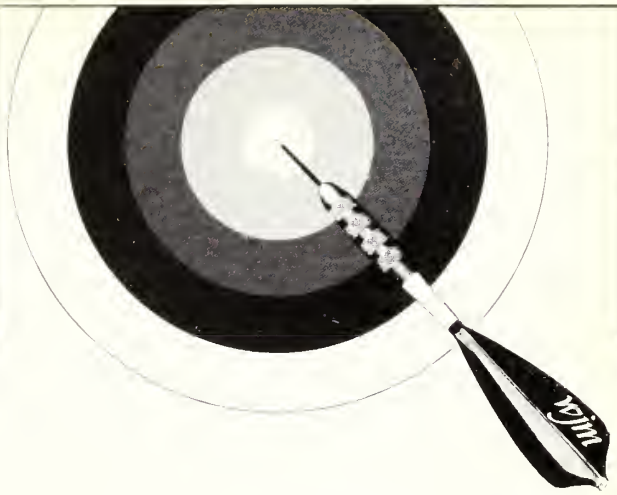

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(Continued from Page 727)

May 6-7—**New Mexico Medical Society Annual Meeting.** The Marshall Building, Albuquerque. Fri-Sat. Contact: Elsa Hall, 7770 Jefferson NE, Suite 400, Albuquerque 87109. (505) 828-0237.

July 18-22—**Imaging 1994.** Eldorado Hotel, Santa Fe. Mon-Fri. Contact: Dawne Ryals, Ryals & Associates, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

CONTACT INFORMATION

UNM SOM—University of New Mexico School of Medicine, Office of CME, PO Box 713, Albuquerque 87131. (505) 277-3942.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. Accredited institutions wishing to list AMA Category 1 CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, UT 84102; or phone (801) 355-7477. For information on CME accreditation, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution.

January 19-22—**Midwinter Conference on Chest Disease.** Cliff Lodge, Snowbird. Wed-Sat. Contact: ITS.

January 29-February 5—**Richard Lende Winter Neurosurgery Conference.** Cliff Lodge, Snowbird. Sat-Sat. Contact: UANS.

February 4—**Chronic Fatigue Syndrome.** LDS Hospital. Fri. Contact: LDSH.

February 7-11—**Surgical Pathology.** Yarrow Hotel, Park City. Mon-Fri. Contact: UUSM.

February 14-18—**Update in Clinical Microbiology and Immunology.** Yarrow Hotel, Park City. Mon-Fri. Contact: UUSM.

February 17-19—**UOS Annual Winter Ski Meeting.** Yarrow Hotel, Park City. Thurs-Sat. Contact: UOS.

February 17-24—**37th Anesthesiology Update: Anesthesia and the Nervous System.** Snowbird Cliff Lodge. 1 week. Contact: UUSM.

February 23-27—**Physical Medicine and Rehabilitation Update.** Prospector Square Conference Center, Park City. Wed-Sun. Contact: UUSM.

February 27-March 2—**35th Annual OB/GYN Update.** Yarrow Hotel, Park City. Sun-Wed. Contact: UUSM.

March 2-5—**Surgical Oncology Update.** Yarrow Hotel, Park City. Wed-Sat. Contact: UUSM.

March 6-11—**Advances in Internal Medicine.** Cottonwood Center, Snowbird. Sun-Fri. Contact: UUSM.

March 8-12—**Microsurgery Workshop.** University Park Hotel, Salt Lake City. Thurs-Sat. Contact: UUSM.

March 11-12—**Western Intermountain Neurological.** University Park Hotel, Salt Lake City. Fri-Sat. Contact: UUSM.

MEDICAL GRAND ROUNDS

Weekly—Internal Medicine Grand Rounds, Psychiatry Grand Rounds, OB/GYN Grand Rounds, Pediatric Grand Rounds. Contact: UUSM, Office of CME, (801) 581-8664.

SPONSORS OF COURSES—ABBREVIATIONS

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DM: Dixie Medical Center, 544 S 400 East, St George 84770. (801) 634-4000.
ETS: Emergency Training Services, 777 N 390 East, American Fork 84003. (801) 763-3555.
FHP: FHP of Utah, 35 W Broadway, Salt Lake City 84101. (801) 355-1234
ITS: Intermountain Thoracic Society, 1616 S 11th East, Salt Lake City 84105. (801) 484-4456.
LDSH: LDS Hospital, 8th Ave and "C" St, Salt Lake City 84143. (801) 321-1100.
LRH: Logan Regional Hospital, 1400 N 5th East, Logan 84321. (801) 752-2050.
MDH: McKay-Dee Hospital Center, 3939 Harrison Blvd, Ogden 84409. (801) 625-2694.
MVH: Mountain View Hospital, 1000 E Highway 6, Payson 84651. (801) 465-9201.
OSS: Ogden Surgical-Medical Society, PO Box 9311, Ogden 84409.
PCMC: Primary Children's Medical Center, 100 N Medical Dr, Salt Lake City 84113. (801) 588-2000.
PVH: Pioneer Valley Hospital, 3460 S 4155 West, West Valley City 84120. (801) 968-9061.
UANS: Utah Association of Neurological Surgeons, 24 South 1100 East, Suite 302, Salt Lake City 84102. (801) 531-7806.
UMIA: Utah Medical Insurance Association, 540 E 500 South, Salt Lake City 84102. (801) 531-0375.
UMA: Utah Medical Association, 540 E Fifth South, Salt Lake City 84102. (801) 355-7477.
UOS: Utah Ophthalmological Society, 540 E 500 South, Salt Lake City 84102. (801) 355-7477.
USH: Utah State Hospital, PO Box 270, Provo 84603-0270. (801) 373-4400.
UUSM: University of Utah School of Medicine, Office of Continuing Medical Education, 50 N Medical Dr, Salt Lake City 84132. (801) 581-8664.
VAMC: Veterans Administration Medical Center, 500 Foothill Dr, Salt Lake City 84148. (801) 582-1565.

WASHINGTON

The listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here, please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 1100, Seattle, WA 98121; or phone (206) 441-9762 or (800) 552-0612.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

January 20—**Law and Medicine Symposium.** Tacoma. Thurs. Contact: PCMS CME.

January 22—**Orthopedic Update.** Seattle. Sat. Contact: Children's Hospital, (206) 526-2501.

February 12-16—**WAPA Board Certification Review Course.** Seattle. Sat-Wed. Contact: Washington Academy of Physician Assistants, (206) 441-9762.

February 25—**Review of HIV Infections.** Tacoma. Fri. Contact: PCMS CME.

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104. (206) 223-5953.
PCMS CME—Contact: Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.
U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.
VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 223-6898.
WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Suite 1100, Seattle, WA 98121. (206) 441-9762.

WYOMING

June 9-11—**Wyoming Medical Society—Annual Meeting.** Jackson Lake Lodge, Moran. Thurs-Sat. Contact WMS, PO Drawer 4009, Cheyenne 82003-4009. (307) 635-2424. ◆

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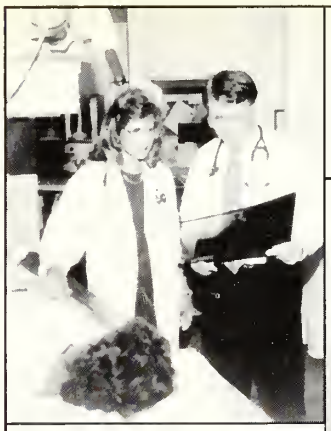

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(Continued on Page 733)

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(Continued from Page 732)

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(Continued on Page 734)

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Colorado Medical Society–PO Box 17550, Denver 80217-0550. (303) 779-5455. Annual Meeting: September 7-11, 1994, Aspen.

Hawaii Medical Association–1360 S Beretania, Honolulu 96814. (808) 536-7702. Annual Meeting: October 7-9, 1994, Ritz-Carlton Maunalani, Hawaii.

Idaho Medical Association–305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888. Annual Meeting: July 28-30, 1994, Sun Valley.

Montana Medical Association–2012 11th Ave, Suite 12, Helena 59601. (406) 443-4000. Annual Meeting: September 29-October 1, 1994, Holiday Inn, Great Falls.

Nevada State Medical Association–3660 Baker Lane, Reno 89502. (702) 825-6788. Annual Meeting: April 21-24, 1994, Coronado, California.

New Mexico Medical Society–7770 Jefferson NE, Suite 400, Albuquerque 87109. (505) 828-0237. Annual Meeting: May 5-7, 1994, Society Office, Albuquerque.

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Indications and Usage *Augmentin* is indicated in the treatment of infections caused by susceptible strains of the designated organisms in the conditions listed below

Lower Respiratory Tract Infections caused by β lactamase-producing strains of *Hemophilus influenzae* and *Moraxella (Branhamella) catarrhalis*

Otitis Media caused by β lactamase-producing strains of *Hemophilus influenzae* and *Moraxella (Branhamella) catarrhalis*

Sinusitis caused by β lactamase producing strains of *Hemophilus influenzae* and *Moraxella (Branhamella) catarrhalis*

Skin and Skin Structure Infections caused by β lactamase-producing strains of *Staphylococcus aureus*, *E. coli* and *Klebsiella* spp.

Urinary Tract Infections caused by β lactamase producing strains of *E. coli*, *Klebsiella* spp. and *Enterobacter* spp.

While *Augmentin* is indicated only for the conditions listed above, infections caused by ampicillin-susceptible organisms are also amenable to *Augmentin* treatment due to its amoxicillin content. Therefore, mixed infections caused by ampicillin-susceptible organisms and β lactamase producing organisms susceptible to *Augmentin* should not require the addition of another antibiotic.

Bacteriological studies, to determine the causative organisms and their susceptibility to *Augmentin*, should be performed together with any indicated surgical procedures.

Therapy may be instituted prior to obtaining the results from bacteriological and susceptibility studies to determine the causative organisms and their susceptibility to *Augmentin* when there is reason to believe the infection may involve any of the β lactamase-producing organisms listed above. Once the results are known, therapy should be adjusted, if appropriate.

Contraindications A history of allergic reactions to any penicillin is a contraindication.

WARNINGS SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTOID) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY. ALTHOUGH ANAPHYLAXIS IS MORE FREQUENT FOLLOWING PARENTERAL THERAPY, IT HAS OCCURRED IN PATIENTS ON ORAL PENICILLINS. THESE REACTIONS ARE MORE LIKELY TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR A HISTORY OF SENSITIVITY TO MULTIPLE ALLERGENS. THERE HAVE BEEN REPORTS OF INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS. BEFORE INITIATING THERAPY WITH ANY PENICILLIN, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS OR OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, *AUGMENTIN* SHOULD BE DISCONTINUED AND THE APPROPRIATE THERAPY INSTITUTED. **SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE, OXYGEN, INTRAVENOUS STEROIDS AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.**

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including *Augmentin*, and has ranged in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of "antibiotic associated colitis."

Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation and treatment with an antibacterial drug clinically effective against *C. difficile* colitis.

Precautions General While *Augmentin* possesses the characteristic low toxicity of the penicillin group of antibiotics, periodic assessment of organ system functions, including renal, hepatic and hematopoietic function, is advisable during prolonged therapy.

A high percentage of patients with mononucleosis who received ampicillin develop a skin rash. Thus, ampicillin-class antibiotics should not be administered to patients with mononucleosis.

The possibility of superinfections with mycotic or bacterial pathogens should be kept in mind during therapy. If superinfections occur (usually involving *Pseudomonas* or *Candida*), the drug should be discontinued and/or appropriate therapy instituted.

Drug Interactions Probenecid decreases the renal tubular secretion of amoxicillin. Concurrent use with *Augmentin* may result in increased and prolonged blood levels of amoxicillin.

The concurrent administration of allopurinol and ampicillin increases substantially the incidence of rashes in patients receiving both drugs as compared to patients receiving ampicillin alone. It is not known whether this potentiation of ampicillin rashes is due to allopurinol or the hyperuricemia present in these patients. There are no data with *Augmentin* and allopurinol administered concurrently.

Augmentin should not be co-administered with Antabuse® (disulfiram).

Carcinogenesis, Mutagenesis, Impairment of Fertility Long-term studies in animals have not been performed to evaluate carcinogenic or mutagenic potential.

Pregnancy (Category B) Reproduction studies have been performed in mice and rats at doses up to ten (10) times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to *Augmentin*. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery Oral ampicillin-class antibiotics are generally poorly absorbed during labor. Studies in guinea pigs have shown that intravenous administration of ampicillin decreased the uterine tone, frequency of contractions, height of contractions and duration of contractions. However, it is not known whether the use of *Augmentin* in humans during labor or delivery has immediate or delayed adverse effects on the fetus, prolongs the duration of labor or increases the likelihood that forceps delivery or other obstetrical intervention or resuscitation of the newborn will be necessary.

Nursing Mothers Ampicillin-class antibiotics are excreted in the milk, therefore caution should be exercised when *Augmentin* is administered to a nursing woman.

Adverse Reactions *Augmentin* is generally well tolerated. The majority of side effects observed in clinical trials were of a mild and transient nature and less than 3% of patients discontinued therapy because of drug-related side effects. The most frequently reported adverse effects were diarrhea/loose stools (9%), nausea (3%), skin rashes and urticaria (3%), vomiting (1%) and vaginitis (1%).

The overall incidence of side effects, and in particular diarrhea, increased with the higher recommended dose. Other less frequently reported reactions include: abdominal discomfort, flatulence and headache.

The following adverse reactions have been reported for ampicillin-class antibiotics:

Gastrointestinal: Diarrhea, nausea, vomiting, indigestion, gastritis, stomatitis, glossitis, black "hairy" tongue, enterocolitis and pseudomembranous colitis. Onset of pseudomembranous colitis symptoms may occur during or after antibiotic treatment (see WARNINGS).

Hypersensitivity reactions: Skin rashes, urticaria, angioedema, serum sickness-like reactions (urticaria or skin rash accompanied by arthritis/arthralgia, myalgia, and frequently fever), erythema multiforme (rarely Stevens-Johnson Syndrome), and an occasional case of exfoliative dermatitis have been reported. These reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids. Whenever such reactions occur, the drug should be discontinued, unless the opinion of the physician dictates otherwise. Serious and occasional fatal hypersensitivity (anaphylactic) reactions can occur with oral penicillin (see WARNINGS).

Liver: A moderate rise in AST (SGOT) and/or ALT (SGPT) has been noted in patients treated with ampicillin-class antibiotics but the significance of these findings is unknown. Hepatic dysfunction, including increases in serum transaminases (AST and/or ALT), serum bilirubin and/or alkaline phosphatase, has been infrequently reported with *Augmentin*. The histologic findings on liver biopsy have consisted of predominantly cholestatic, hepatocellular or mixed cholestatic-hepatocellular changes. The onset of signs/symptoms of hepatic dysfunction may occur during or after therapy. Complete resolution has occurred with time.

Hemic and Lymphatic Systems: Anemia, thrombocytopenia, thrombocytopenic purpura, eosinophilia, leukopenia and agranulocytosis have been reported during therapy with penicillins. These reactions are usually reversible on discontinuation of therapy and are believed to be hypersensitivity phenomena. A slight thrombocytosis was noted in less than 1% of the patients treated with *Augmentin*.

Central Nervous System: Reversible hyperactivity, agitation, anxiety, insomnia, confusion, behavioral changes, and/or dizziness have been reported rarely.

BRS:AG L5A

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When you suspect ß-lactamase-resistant bronchitis and pneumonia*

The bugs stop here

AUGMENTIN®

amoxicillin/clavulanate potassium

Augmentin®: 8 years of undiminished efficacy[1]

- Clinical response rate of 98% in bronchitis and pneumonia[2]
- Latest† *in vitro* susceptibility‡: still impressive – *H. influenzae*: 100% and *M. catarrhalis*: 99.8%[3]
- Actively destroys ß-lactamase[4,5]

* For susceptible strains of indicated organisms. *Augmentin* is appropriate initial therapy when you suspect ß-lactamase-producing organisms.

† Latest available annual data January to December 1991

‡ *In vitro* susceptibility does not necessarily imply *in vivo* efficacy.

Please see brief summary of prescribing information for contraindications, warnings, precautions and adverse reactions on adjacent page.

References: 1. Neu HC, Wilson APR, Gruneberg RN: Amoxicillin/clavulanic acid — a review of its efficacy in over 38,500 patients from 1979 to 1992. *J Chemother* 1993. In press. **2.** Data on file, SmithKline Beecham Pharmaceuticals. **3.** Data from the Institutes for Microbiology Research, Franklin, Tenn. **4.** Brown R, Pinkerton R, Tuttle M: Respiratory infections in smokers. *Am Fam Physician* 1987;36:133-140. **5.** Neu HC: Contribution of beta-lactamases to bacterial resistance and mechanisms to inhibit beta-lactamases. *Am J Med* 1985;79(suppl 5B):2-12

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